THE CONTRIBUTION OF ATOMIC ENERGY TO MEDICINE

HEARINGS

BEFORE THE

SUBCOMMITTEE ON RESEARCH AND DEVELOPMENT

OF THE

JOINT COMMITTEE ON ATOMIC ENERGY

CONGRESS OF THE UNITED STATES

EIGHTY-THIRD CONGRESS

SECOND SESSION

ON

THE CONTRIBUTION OF ATOMIC ENERGY TO MEDICINE

JUNE 2, 3, AND 4, 1954

Printed for the use of the Joint Committee on Atomic Energy

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FROM
E. Y. BERRY
U. S. REPRESENTATIVE
SOUTH DAKOTA

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(Created pursuant to Public Law 585, 79th Cong.)

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THE CONTRIBUTION OF ATOMIC ENERGY TO MEDICINE

WEDNESDAY, JUNE 2, 1954

CONGRESS OF THE UNITED STATES,
JOINT COMMITTEE ON ATOMIC ENERGY,
SUBCOMMITTEE ON RESEARCH AND DEVELOPMENT,
Washington, D. C.

The joint committee met, pursuant to call, at 2:20 p. m., in the caucus room, Old House Office Building, Hon. Carl Hinshaw (chairman of the subcommittee), presiding.

Present: Representatives Hinshaw (presiding) and Durham.

Professional staff member: Edward L. Heller.

Representative HINSHAW. The meeting will come to order.

With this meeting of the Research and Development Subcommittee of the Joint Committee on Atomic Energy, we are beginning 3 days of public hearings dealing with the uses of atomic energy in medical research and therapy.

Earlier this year our subcommittee heard detailed testimony on the application of atomic energy in the field of agriculture. I think those hearings helped underscore the fact that the peaceful potentialities of atomic energy will prove in the long run to be more important for the people of the world than military uses of the atom which now hold the spotlight. Over 16,000 printed copies of the agriculture hearings have been distributed to individuals throughout this country who requested them, and over 4,000 copies have been purchased by agencies of our Government and other governments for distribution throughout the world.

Today we take up the field of medical research, a subject of vital importance to each and every one of us, and one in which the fruits of our atomic-energy effort are already making important contributions. Through atomic energy we have gained powerful new tools with which to attack those scourges of humanity—cancer, heart disease, arthritis, and certain chronic illnesses—which cause so much suffering in this world.

While these new atomic research and treatment techniques will not singlehandedly produce successful results overnight, and while we must not expect miracles, they do constitute a powerful addition to the arsenal of medical science in its fight to protect mankind from disease.

The doctors and scientists who will discuss atomic medicine with us during these hearings are a part of the great army of science which is working for the welfare of mankind through medical research.

It is a particular pleasure, therefore, to inaugurate these hearings in which both Members of the Congress and the public will have an

opportunity to obtain firsthand information from the doctors and scientists who are devoting their great talent to the medical application of the atom.

These gentlemen have come from many parts of the country. They have interrupted vital and important work so that we may be better informed and thus come to appreciate the truly great contributions of the peaceful atom to the welfare of mankind.

Before we call our first witness I would like to insert in the record at this point, the correspondence between Chairman Strauss of the Atomic Energy Commission and myself concerning these hearings.

(The correspondence referred to follows:)

MAY 13, 1954.

UNITED STATES ATOMIC ENERGY COMMISSION,
Washington 25, D. C.

GENTLEMEN: On February 4, 1954, at an executive hearing before the Research and Development Subcommittee, Dr. Bugher reported on the biology and medicine program of the Commission. At the conclusion of this meeting, the subcommittee chairman requested that the Commission prepare a series of public hearings devoted to the peacetime applications of atomic energy. The first such hearing concerning the contributions of atomic energy to agriculture was presented before the subcommittee at public hearings on March 31 and April 1.

The subcommittee would now like to request that the Commission present a discussion of the contributions of atomic energy to medicine at public hearings before the Research and Development Subcommittee at 2 p. m. on June 1 and 2.

The Commission did an outstanding job in preparing its program on the contribution of atomic energy to agriculture as is witnessed by the fact that Members of Congress have requested over 12,000 copies of the hearings for distribution to constituents who are concerned with agriculture. I am therefore looking forward with keen anticipation to the Commission's program on the contributions of atomic energy to medicine since this is an area which affects everyone of us in a very personal way.

I understand that the Commission staff has been working with the committee staff on the details of this program. The Commission will be notified as soon as the hearing room has been finally decided upon.

Sincerely yours,

CARL HINSHAW,
Chairman, Subcommittee on Research and Development.

UNITED STATES ATOMIC ENERGY COMMISSION,
Washington, D. C., May 28, 1954.

Hon. CARL HINSHAW,
Chairman, Subcommittee on Research and Development,
Joint Committee on Atomic Energy, Congress of the United States.

DEAR MR. HINSHAW: This will acknowledge your letter of May 13, 1954, regarding public hearings to be held on June 2 and 3, 1954, before the Subcommittee on Research and Development of which you are chairman.

Dr. John C. Bugher, Director of the Division of Biology and Medicine, will represent the Atomic Energy Commission at these hearings. He informs me that arrangements are being made with the staff of the subcommittee regarding the agenda and the scientists who will be asked to appear.

The Commission is pleased to have the opportunity to present additional evidence of the progress which is being made in utilizing atomic energy for the benefit of man.

Sincerely yours,

/s/ Lewis L. Strauss,
LEWIS L. STRAUSS,
Chairman.

STATEMENT OF DR. JOHN C. BUGHER, DIRECTOR, DIVISION OF BIOLOGY AND MEDICINE, ATOMIC ENERGY COMMISSION

Representative HINSHAW. Now Dr. John C. Bugher, from whom we have heard before, the eminent Director of the Division of Biology and Medicine of the Atomic Energy Commission, an M. D. of the University of Michigan, of which I have the honor also to be an alumnus; an honorary doctor of science of Taylor University; professor of pathology at the University of Michigan from 1929 to 1937; staff member of the international health division of the Rockefeller Foundation since 1937, engaged in research in the control of infectious diseases, including work on the control of yellow fever in the South American and African Continents, and the control of other tropical virus diseases; director of research in the control of yellow fever in Bogota, Colombia, 1941 to 1943; established and directed yellow fever research institute at Lagos, Nigeria. He has many publications in the field of pathology, including cancer, yellow fever, and other virus diseases.

Dr. Bugher, we are delighted to hear from you again concerning this vital subject—the objective of the medical program of the Atomic Energy Commission.

Dr. BUGHER. Mr. Chairman, we have the honor to appear before you again to continue our story of the contributions of atomic energy to the general benefits of man, and today with particular reference to the field of medicine.

As you may recall, in discussing the applications to agriculture at the time of the first hearing, it was made very clear that the concern with living things and with life processes does not permit one to make sharp boundary distinctions between the various scientific disciplines, and many of the phenomena which are of particular interest to the agriculturalist likewise come to bear on the problems of disease in the human being. And, conversely, many of the medical developments are of profound importance and significance to the expert in animal diseases and to those who are interested in biology generally.

Consequently, these various fields do not sharply separate themselves one from another, and we continue, therefore, our discussion in very much the same general orientation as before.

In the establishment by the Congress of the Atomic Energy Commission and under the law which brought our entire atomic-energy program into being, there was very clearly the concept and the intent that atomic energy would be exploited to its utmost, not merely for defensive purposes but with regard to all of the capabilities for human welfare and general betterment. There was placed upon the Commission, the Commissioners, and on all of us, this broad responsibility to deliver to the extent of our capability the maximum development of atomic energy at the maximim speed. We have attempted to do that, and within the limits of human frailty we have expended our best efforts to meet this requirement placed upon us by the Congress.

During this hearing we hope to lay before you the perspective which has developed over these few years in the scientific character of the medical program. We would like to make clear something of the impact which this program has had upon the whole picture of American medicine, to bring into sharp focus the enormous acceleration in the acquisition of knowledge of medical problems, an acceleration which I think may be conservatively stated to be of the order of a

quarter of a century. By that I mean that through the utilization of nuclear reactions and all of the other aspects of nuclear science the scope of medical knowledge has been advanced, I should think, more than 25 years over what it otherwise would have been.

So that is the perspective which we wish to develop. And while it is impossible to give credit to all who merit it, I think that the Joint Committee on Atomic Energy and the Appropriations Committees of the two Chambers of Congress should have a lively satisfaction in the program that they have made possible and have brought, in fact, into being.

Now, in the approach which the Commission has made, it has been recognized, first, that there is a responsibility for the welfare and the safety of all those concerned with the atomic-energy operations. Second, there has been the additional responsibility for advancing our fundamental knowledge of the character of all life processes.

You will find, therefore, that the discussion of this hearing will revolve around three broad aspects of the application of atomic energy to medicine.

One is the advancement of knowledge of biological processes themselves, through all the means of application of nuclear science.

The second comes closer to the individual patient and deals with the utilization of atomic-energy techniques in the diagnoses of disease.

The third aspect is the utilization of our capabilities in the treatment of disease in many different forms.

Now, as we examine this entire field one finds it somewhat difficult to pull apart the components and contributing elements because one finds that any one line of investigation and extension of knowledge has developed many branches; so that there is no aspect of medicine today that has not felt in some degree the impact of this entire program.

To carry on the research which has been underway, the Commission has developed a number of medical research centers at the national laboratories, such as at Brookhaven on Long Island, at the Argonne National Laboratory in Chicago, at Oak Ridge, and at Los Alamos; and, furthermore, certain large university installations, such as those at the University of California at Berkeley and Los Angeles, as well as the University of Rochester at Rochester, N. Y. There are many more. Those are the chief examples.

In this effort, the research directly supported by the Division of Biology and Medicine itself during this year involves more than 1,700 scientists in national laboratories and in over 150 universities of the country in which the program is conducted. These figures, of course, include all of the research, whether devoted to biology generally or to medicine specifically.

But the Commission's ambition has been not to exert a monopoly in any sense, but to support, to assist, and to encourage medical research by all groups of people who may be competent to participate. In addition to the investigations directly supported by the Commission, it has encouraged the use of atomic-energy products by research organizations of all kinds, in all institutions, and throughout every portion of our land.

Consequently, as we will hear during these 3 days from various members of our large number of colleagues, there are very many different

facets to this entire program. They have endless ramifications. But we will attempt to make some accounting of what has been accomplished, of what is going on, and, finally, of what we have sound reason to expect in the very near future.

Thank you, sir.

Representative HINSHAW. Thank you, Dr. Bugher.

The response of the pathologists and the medical men of America has been most admirable, and we have hopes for great things in the future.

STATEMENT OF DR. SHIELDS WARREN, DIRECTOR, CANCER RESEARCH INSTITUTE, NEW ENGLAND DEACONESS HOSPITAL, BOSTON, MASS.

Representative HINSHAW. Now to give a description of the early days of the atomic energy program in medical research, we have Dr. Shields Warren, director of the Cancer Research Institute of the New England Deaconess Hospital of Boston, Mass., and deputy chairman of the Advisory Committee for the Division of Biology and Medicine of the Atomic Energy Commission.

Dr. Warren is a native of Cambridge, Mass. He is a graduate of Boston University; received his medical doctorate degree from Harvard University and an honorary doctor of science degree from Boston University. Dr. Warren is professor of pathology at Harvard University and pathologist to the Harvard Cancer Commission. He is on the Scientific Advisory Board of the Chief of Staff of the United States Air Force; research consultant in pathology to the United States Navy; and expert consultant to the Surgeon General; on the Scientific Advisory Board of the Armed Forces Institute of Pathology. He is the consultant and past member of the National Advisory Cancer Council; a member of the National Research Council, serving in various capacities, including Chairman of the Committee on Atomic Casualties. He has been president of the American Society for Experimental Pathology and the American Association for Cancer Research. He served in the United States Navy as a captain during World War II, and was one of the leaders of the joint commission to assess the effects of the atomic bomb in Japan in 1945.

Dr. Warren was the first Director of the Division of Biology and Medicine, and with Dr. Alan Gregg, the first Chairman of the Advisory Committee for Biology and Medicine, these were the two persons principally responsible for the successful initiation of the Atomic Energy Commission's program in this area. Dr. Shields Warren.

Dr. WARREN. Mr. Hinshaw, ladies and gentlemen, some 7 years ago this month, to be exact, the Atomic Energy Commission, then new, appointed a Medical Board of Review to check over the work that had been accomplished by the Manhattan Engineering District during its responsibility for the development of atomic energy and, in addition, to make recommendations as to the future medical program of the atomic energy field.

This Medical Board of Review, composed of distinguished leaders in the field, was a very effective organization, setting a pattern which has been largely followed up to the present time.

It is of interest, therefore, to see some of the things that they had recommended, some of the things that have been accomplished, and, as you will hear later, some of the things now underway in this field of medical applications of atomic energy.

First, the Medical Board of Review found that a splendid job had been done in protecting the health of the workers and the health of those adjacent to the plants of the Atomic Energy Commission and its contractors. The fine record, I am happy to say, is being continued.

Second, they recognized that this new force had very broad applications in medicine and in biology that required not only new tools for its utilization, its development, but, even more fundamental than that, required new research workers, people who were not then available, trained to carry out the new explorations that this means of energy offered.

Consequently, they laid great stress on the training of personnel to work in this new field, and further on the development of resources in the great universities throughout this country, so that not only the finished research worker could be acquainted with this field, but also the students who will provide the medical research workers of the future could also come in contact with it.

One of the early problems was the question of secrecy in the field of atomic energy. Fortunately, the vast bulk of information required in the field of biology and of medicine is of such a nature that it can be made fully and freely available to mankind without endangering the security of the country; and it has been possible with only very slight interference from the standpoint of security to make these major advances that will be presented to you in the course of these hearings.

One of the first things to do was to get some of these new tools that atomic energy made available into the hands of scientists, and this was particularly true in the case of radioisotopes. The radioisotopes, you will recall, are elements which have the chemical properties of the ordinary form of the element and behave just as the ordinary element does in all regards except that they are radioactive. Thus they can be readily traced, as they will carry radioactivity wherever they may be carried by the vital process.

Consequently, this provides an extraordinary useful tool for following vital processes and for producing curative radiation, not only from the outside, as was done by X-rays and radium in the past, but internally as well.

These isotopes, because of their radioactive properties are potentially dangerous, and it was necessary that there be instrumentation developed so that they could be detected—and the simple Geiger-Müller counter has been so improved that today it is in one form a rough and ready field tool of the uranium prospector as well as in another an elaborate instrument for very careful measurement in the laboratory. In addition, other types of instruments for the detection of radiation have been evolved, so that we can deal safely with this new force and study it in quantitative fashion.

Furthermore, it is possible with this means of instrumentation to detect very minute changes in the vital processes that are of importance from the standpoint of medicine.

It was also necessary, along with the instruments and isotopes, to provide opportunity for those physicians who had not been acquainted

with these substances to learn how to use them. And so at Oak Ridge a school in the biologic and medical utilization of isotopes was established, which is still continuing. It has many distinguished graduates, among them many of the medical leaders of the present day.

It was important that this knowledge should be widely disseminated, and so, in addition, a special training program was evolved in the field of health physics, as this type of measurement of radiation is called and, furthermore, four centers were set up in different parts of the country away from these national laboratories that Dr. Bugher has mentioned earlier. These centers, in North Carolina, in Texas, in Colorado, and in Oregon, are providing a continuing source of scientists for work in the field, just as many other universities are doing at the present day.

One of the interesting sidelights of the renewed interest in nuclear physics was that not only were there these startling new developments in the way of finding radioactive materials, creating them, utilizing them, but in addition the whole field of nuclear science received a great transfusion of interest and effort. Thus X-ray apparatus that had remained relatively static for a period of some years was rapidly advanced and improved, and new types of sources of radiation such as the linear accelerator were evolved. There were marked improvements in the cyclotron, which had already existed in the preatomic age and was one of the important factors in the development of atomic energy.

So there has been widespread advance in the means by which the physical forces of radiation could be applied to medicine in these other lines as well as along the line of radioisotopes.

Special interest rests in the use of these radioactive isotopes in medicine and in biology, because they provide means of giving us in detail what the vital processes are.

Some years ago you could have seen growing in a hermetically sealed chamber at the Argonne National Laboratory some of the foxglove plants.

Representative HINSHAW. Am I right, that is digitalis?

Dr. WARREN. This is what digitalis comes from.

Representative HINSHAW. Thank you.

Dr. WARREN. The radiocarbon in the form of radiocarbon dioxide had been added to the atmosphere in which this plant was growing, and this plant incorporated into the digitalis radioactive carbon so that the drug could be followed in its pharmacological action in greater detail than had ever been done previously.

This type of biologic synthesis involving various of the elements so that we can trace some of the important complex organic substances and learn how they work in the field of medicine has been carried out successfully again and again, and is a technique that doctors and biologists have available at the present time.

Representative HINSHAW. I understand that Dr. Geiling will speak on that subject particularly at tomorrow's hearing.

Dr. WARREN. Yes. He is most expert in this field of the pharmacological applications of these substances. So I will not go into any detail, but I did want to speak of this phase of the utilization of atomic energy.

In addition, it has been possible to follow the vital processes in a way that has never been feasible before. For example, when an individual utilizes sugar in his body, it provides an important source of energy. When he does not use sugar properly in his body, he is a victim of the disease known as diabetes. A great deal of chemical studies have been carried on the fifty-odd years that this disease has been studied intensively, but there was no clear understanding of how the sugar was utilized until the investigations with radioactive carbon incorporated into the sugar molecule could be carried out. We understand much more clearly now how this utilization of sugar is being carried through. This will mean much to the many diabetic patients of the present day.

I could multiply examples in the research field, but let us look instead at some of the problems more immediately applicable to the patients now ill in our hospitals.

One of the fairly frequent causes of illness is the disorder of the thyroid gland. The thyroid gland takes up iodine very avidly. By the use of radioactive iodine one can diagnose the type of disorder of the thyroid gland from which a patient is suffering with a greater degree of accuracy than practically any other means.

The activity of the thyroid used to be determined very largely by the measurement of the carbon dioxide excreted by the lungs, but it is much simpler, rather than using this basal metabolic test, if one has radioactive iodine available. It is much more accurate to determine the uptake of radioactive iodine in the thyroid, and this gives a very clear clue to the type of thyroid disease from which the patient is suffering.

Radioactive iodine is also useful in therapy. Quite early in trying to see what could be done with these new substances, radioactive iodine, radioactive phosphorus, and radioactive gold came into use. You will hear more about these various substances from others later. I merely wish to call to your attention these substances that were utilized early in this research program and have helped to clear the broad road along which medical research is now sweeping with the aid of atomic energy.

Thank you.

Representative HINSHAW. We thank you, sir. That was a very fine exposition of the program of the Atomic Energy Commission and of science.

STATEMENT OF DR. JOHN HUNDALE LAWRENCE, DIRECTOR, DONNER LABORATORY, UNIVERSITY OF CALIFORNIA, BERKELEY, CALIF.

Representative HINSHAW. We will now have a discussion of the so-called horse-and-buggy days of radioisotopes in medical research by Dr. John Hundale Lawrence, director of the Donner Laboratory of Medical Physics of the University of California at Berkeley, Calif. Dr. Lawrence was born in Canton, S. Dak., and he received his bachelor of arts degree from the University of South Dakota, his doctorate of medicine at Harvard Medical School, and was awarded an honorary doctor of science degree by the University of South Dakota.

Dr. Lawrence is the first person ever to use artificially produced radioactive isotopes in the treatment of human disease. He was associated with the Office of Scientific Research and Development during World War II and with the medical activities of the Manhattan District. He is a member of many learned societies and recipient of the Caldwell Medal of the American Roentgen Ray Society, and of the Davidson Medal of the British Institute of Radiology. He has been Kreschmer lecturer at the Institute of Medicine, Chicago; Davidson lecturer at London; William H. Welch lecturer and Ludwig Kast lecturer before the New York Academy of Medicine.

Dr. Lawrence will talk about the early days of the use of radioisotopes before they became available in essentially unlimited quantities, and will discuss some of his laboratory's current activities. We are happy to greet you, Dr. Lawrence.

Dr. LAWRENCE. Thank you, sir.

Mr. Chairman and ladies and gentlemen, the horse-and-buggy days of atomic energy actually do not go back to the real horse-and-buggy days, because this goes back only to about 1934, and that is a time when the first cyclotron was producing adequate quantities of radioactive materials so that those of us who were fortunate to be around one of these cyclotrons could once in a while succeed in persuading some of our physicist colleagues, i. e., Prof. Ernest O. Lawrence, et al., to stop their atom splitting long enough to manufacture a few of these new isotopes for research in animals and in man. We were not popular around the cyclotron in those days because we were also studying the effects of the new radiations coming from the cyclotron in experiments on animals such as mice and rats, with a view to trying to protect these pioneer workers from damage. So we were not popular, but in the long run we were helpful in preventing injuries to them over the years.

At that time those of us working with these new materials felt, as Prof. A. D. Hill did, that perhaps some day people would look back on the isotope as being as important to medicine as the microscope; and I think now, as Dr. Bugher indicated, since the atomic energy program, that has probably proven to be true.

At that time, in 1934, the radioisotopes were not widely available yet. However, cyclotrons were being built throughout the country and abroad, so that many workers were able to get these materials for experimental use. Yet the big push in this field, as Dr. Warren has pointed out, came from the Second World War and the development through the Manhattan District, and later the Atomic Energy Commission, of the atomic pile and its many benefits; so that now these radioactive materials are widely available throughout the country, and all capable and qualified workers can obtain them.

Although we worked in the horse-and-buggy days at that time, our work was supported chiefly by foundations such as the Rockefeller Foundation, the Research Corp., the Markle Foundation and others. Since that time we have been fortunate in getting further and continuous support from the Atomic Energy Commission.

I would like, during the next 10 or so minutes, to give you examples of current and past research going on in the Radiation Laboratory and the Donner Laboratory in Berkeley, pointing out the applications of some of this work to problems that we are all interested in, such

as aging, diseases of the blood, cancer, and hardening of the arteries, and with the aid of charts I will mention the two techniques—the tracer technique and therapy.

These are the charts and I will go through them very rapidly because I do not want to take more than my allotted 20 minutes.

This shows a setup for the tracing of radioactive compounds in animals or in men. (Exhibit 1, p. 11.) It shows about five scintillation counters which can be placed over various parts of the body, and the uptake of the radioactive compound in various tissues is recorded on the drum and can be torn off and used in interpretation. And the application of this machine, which can be used in studies using gamma ray emitting isotopes, is becoming quite common now in a clinical sense. The type of information that can be obtained is exemplified by this chart, where the counting rate is plotted against time after the injection of radioactive iron.

From this first high curve you can see the great uptake in the bone marrow. That is the counter facing the pelvis, that is, facing a large volume of bone marrow. The other curves are over the liver and the spleen. These are in a normal subject. From this data it is possible to calculate the rate and site of red cell production in normal subjects and in patients with various blood disorders. This technique is helping physicians in certain clinical problems which arise.

Ths next chart shows the counting rate over the spleen (exhibit 2, p. 12), plotted in counting rate against days, in three different types of patients.

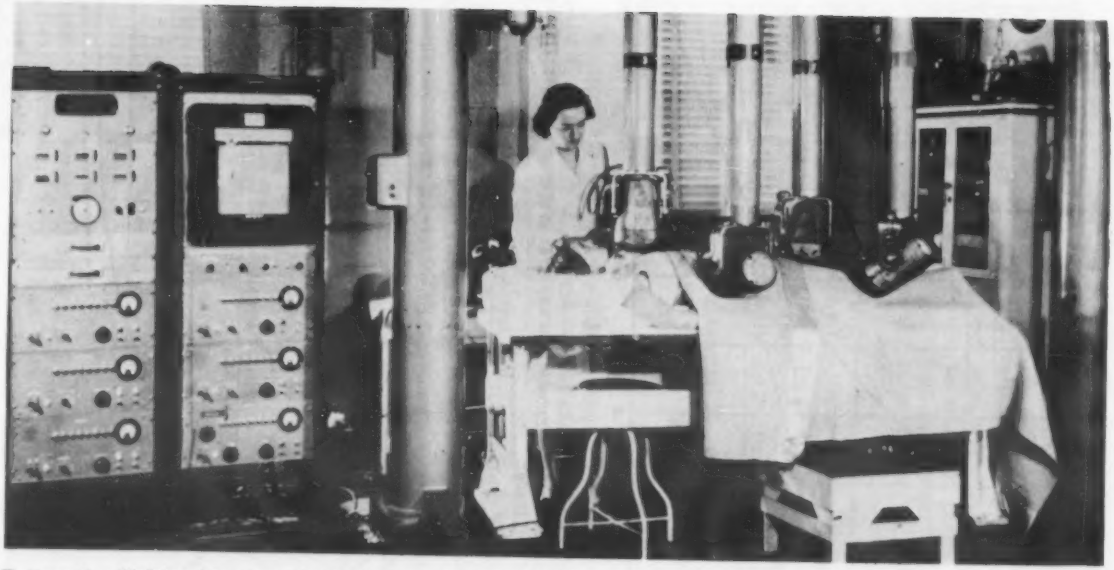

EXHIBIT 1.—Multiport in vivo scintillation counter. This instrument permits detection of gamma-ray emitting radioactive compound uptake in several body tissues at the same time. In this instance the subject has received a tracer quantity of radioactive iron, and the counting rates over the liver, spleen, and bone marrow are being recorded. This instrument adds a valuable diagnostic method to the study of patients with blood disorders such as anemia and polycythemia vera in that it shows the site and rate of red cell production.

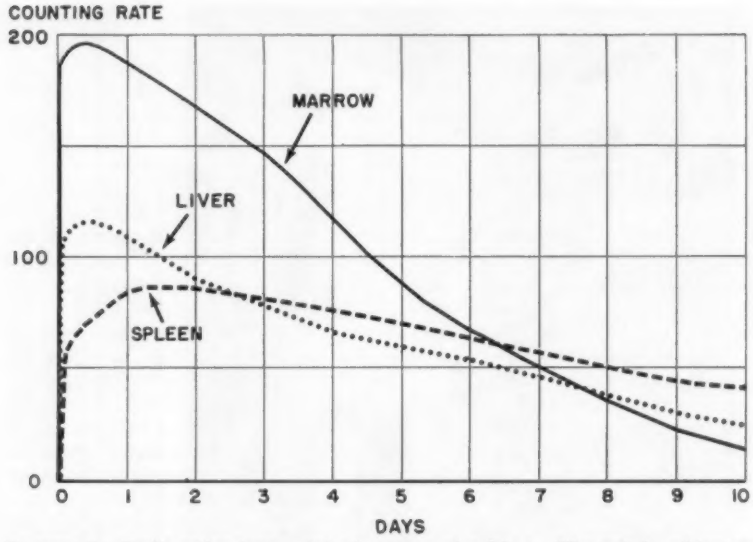

EXHIBIT 2.—Radioactive iron uptake in a normal subject. The uptake of tracer iron over the bone marrow, the spleen, and the liver is shown at various times after injection of the tracer.

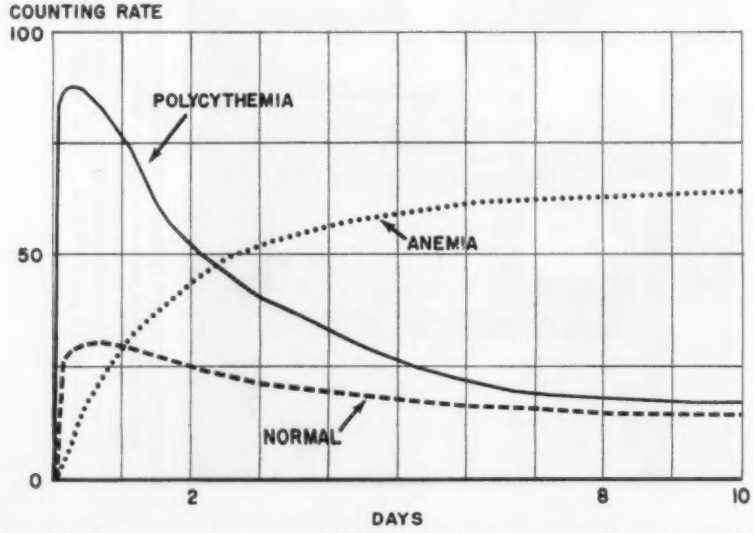

EXHIBIT 3.—Radioactive iron uptake in the spleen plotted against time after injection of tracer iron in a patient with polycythemia vera (green); a patient with refractory anemia (blue); and a normal subject (yellow). In the first instance (green), the spleen curve shows that there is a site of red-cell production in the spleen; in the second, the spleen is destroying red cells at an abnormal rate; in the third, the spleen curve shows the normal rate of uptake.

The first patient, with a high curve, is a patient who is making red cells primarily in the spleen, which is abnormal. The second one is a patient with severe refractory anemia, so-called aplastic anemia. And the third one is the normal one, similar to that in the previous chart. There are occasions in clinical medicine when one must know whether the spleen is making red cells, as indicated in the first curve, the green one, or destroying them, as indicated in the blue curve. One would not want to remove the spleen in a subject whose only source of red-cell production is in the spleen, whereas he might want to remove it if the spleen were destroying red cells at an excessive rate. Since iron is an integral part of red cells, the site and rate of red-cell production can be measured by following the tracer iron.

Representative HINSHAW. I wish you would explain to me one thing. As a pure and very simple layman, I have often heard that the red cells are produced in the marrow of the bone. Now you say they are produced in the spleen.

Dr. LAWRENCE. In some abnormal states. In the first chart, Mr. Chairman, the normal picture showed the primary production of red cells in the bone marrow, that is, in the counter facing the pelvis, which looks at the largest volume of marrow we can look at with a scintillation counter.

There is an abnormal condition here in this other chart (exhibit 3, p. 12) in that the red-cell production is primarily in the spleen, and the bone marrow is fibrotic and osteosclerotic, that is, not producing red cells.

Representative HINSHAW. Those are big, long words.

Dr. LAWRENCE. One's marrow is simply not functioning and the spleen has taken over, fortunately.

Representative HINSHAW. Then there is a duplicate set of organs that supply red-blood cells?

Dr. LAWRENCE. In some instances, yes; some cases.

Representative HINSHAW. I should say duplicating. I did not mean duplicate.

Dr. LAWRENCE. Duplicating, yes.

Representative HINSHAW. Very good.

Dr. LAMRENCE. The next chart, please (exhibit 4, p. 14). I will pass over this very briefly. It shows the extremely small Geiger counters over a mouse with a cancer. There is one counter over the cancer and one over the tissue next to it which is normal, and one over the leg. Cancer tissues can thus be studied and compared with normal tissues. These are extremely small counters with thin mica windows with transverse diameters of about two millimeters.

Radioactive gases are extremely helpful in studying normal and abnormal processes. Here is a subject breathing radioactive carbon monoxide (exhibit 5, p. 15) in work carried on during World War II for the Navy on carbon monoxide poisoning. The radioactive carbon monoxide gas in the bag is breathed and the counters are placed, in this instance, over the lung and the thigh.

Other gases which were used during World War II were applied in the study of high altitude bends and diver's bends. With their use we were able to select flyers who were resistant to the bends.

Representative HINSHAW. I might explain that the people most liable to getting bends are those people who dig tunnels under rivers.

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I learned about that a long time ago when I was a sophomore at Princeton University. We went into the Hudson-Manhattan tubes when they were being constructed and it seemed that as tunnel workers came out from under the pressures that were necessarily generated in order to keep the water out of the tube, and if they came out too fast, they suffered what is known as the bends, which was the collection, as I remember it, of nitrogen in the joints. Is that right?

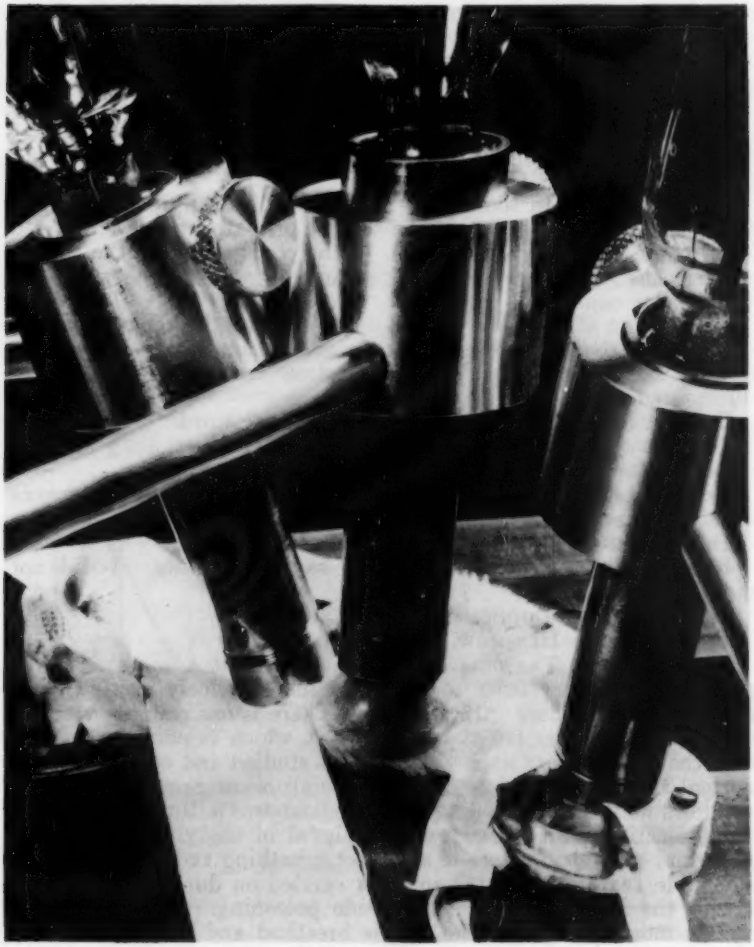

EXHIBIT 4.—Small Geiger counters, with thin mica windows of about 2 millimeter diameter are shown measuring the uptake of a radioactive compound in a cancer and in nearby normal tissue of a tumor-bearing mouse.

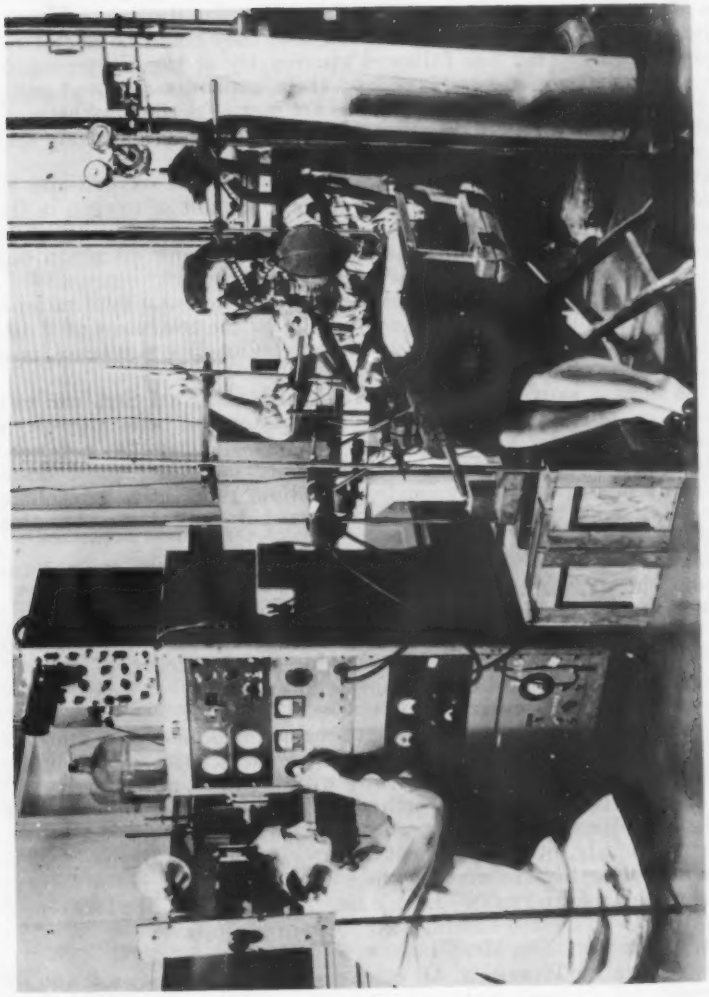

EXHIBIT 5.—Apparatus used for determining the rate of radioactive carbon monoxide gas breathed into the body.

Dr. LAWRENCE. That is correct. Perhaps I do not need to discuss this subject further.

Representative HINSHAW. Not with me, but for the benefit of others you do.

Dr. LAWRENCE. As an interesting byproduct of these investigations it was found in the case of breathing xenon, which is a rare gas in the atmosphere, that some of the subjects became drowsy, and later experiments on rats and mice showed that they could be narcotized with this gas. This was followed up recently at the University of Iowa, when two patients there had their appendix removed using this inert gas—which we know now is not inert—as the anesthetic.

Representative HINSHAW. You mean by anesthetic something that takes the place of oxygen——

Dr. LAWRENCE. In this instance about 20 percent oxygen and 80 percent xenon is used so you have a normal amount of oxygen in the system. But the xenon replaces the other gases normally present in the air and provides the anesthetic effect. This work on xenon was an unexpected byproduct of the research.

Now for a brief moment to pass on to 2 therapeutic applications, beginning in 1936 and brought up to date, on the treatment of 2 diseases based on one's ability to localize a radioactive substance in a tissue which you would want to bombard.

One disease, polycythemia vera, for which Cardinal Stepinac was treated in Yugoslavia, is a condition in which the bone marrow is hyperactive, producing red cells too actively and rapidly, a disease which can be controlled very satisfactorily with infrequent doses either by mouth or intravenously, of sodium radioactive phosphate now being made in the atomic piles for many doctors throughout this country and the world.

Representative HINSHAW. Which is the atomic attack—the sodium or phosphorus?

Dr. LAWRENCE. Phosphorus, P–32.

I will not dwell on this except to point out that in this first group of 201 patients treated and followed for over 15 years, 91 percent have survived and lived comfortably and usefully over 5 years, and 70 percent over 10 years (exhibit 6, p. 17). This life expectancy is equal to or slightly better than that obtained with insulin in diabetes and with liver extract in the treatment of pernicious anemia. This is the first disease treated successfully with artificial radioactivity.

A less satisfactory, but worthwhile, therapeutic application of artificial radioactivity is the use of the same element, P–32, orally or intravenously, in the treatment of chronic leukemia, results which are not exciting but are worth while.

Representative HINSHAW. Let me interrupt you here, Dr. Lawrence. Was it you who treated Cardinal Stepinac in Yugoslavia?

Dr. LAWRENCE. Yes, Mr. Hinshaw.

Representative HINSHAW. Of course, we do not want to ask you to go into detail concerning that, but it is interesting, an interesting fact to have recorded here. I wish you would at least mention it.

Dr. LAWRENCE. His was a classical example of polycythemia vera. His age was 55 and this fits the average age of onset. He has had one treatment with radioactive phosphorus in August of 1953, and he has done very well. We have been in contact with his doctors and

also have had a colleague from Germany visit him recently, and he has responded very satisfactorily.

Representative HINSHAW. I am very glad to hear it.

NO. OF CASES	AVERAGE AGE	MEDIAN SURVIVAL	SURVIVAL TO 5 YEARS	TO 10
201	52	13.2	91.5 %	70

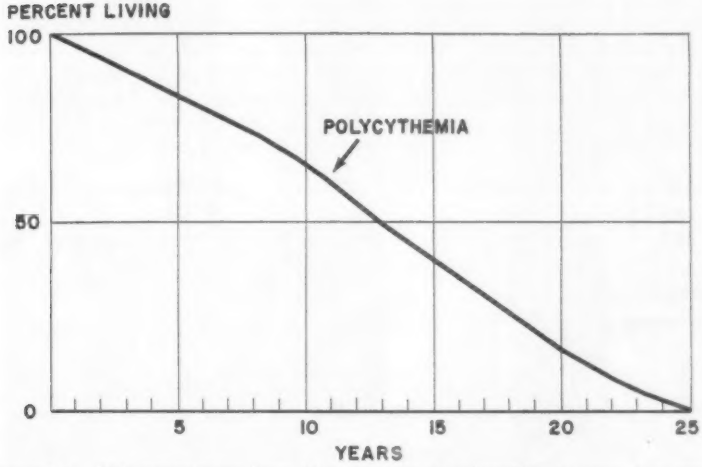

EXHIBIT 6.—Life expectancy from date of onset of polycythemia vera in a group of 201 patients treated with radioactive phosphorus.

Dr. LAWRENCE. The problem of leukemia is a great one, and no one working in artificial radioactivity would want to give the impression that he has done very much for it. However, if one looks at the results with radioactive phosphorus, he can see they are worth while. They are as good as those using any other method, and many workers think that the end results are superior for two reasons: First, these people have no reaction to therapy—and second their lives are prolonged.

Representative HINSHAW. Let me interrupt, Doctor. As I understand it, being a layman, leukemia is a sort of cancer of the blood, is it not?

Dr. LAWRENCE. Yes; it is an overgrowth of the white cells, and some people consider it cancer of the blood.

Representative HINSHAW. That is to say the cells multiply with inordinate rapidity?

Dr. LAWRENCE. Yes, sir.

Representative HINSHAW. And consequently it is considered cancer?

Dr. LAWRENCE. I am hoping that it will prove to be due to some metabolic defect like pernicious anemia, but it may not or may be cancer or cancer-like.

Representative HINSHAW. We have all of these terms we apply to these things.

Dr. LAWRENCE. It is similar to cancer, except in many instances it is a very mild disease and people can live 5, 10, 15, and 20 years comfortably. Mr. Chairman, to show you these results (exhibit 7, below), how good and how bad they are—at 5 years, 54 percent of these people are living and well; and the average duration of the whole group is 5.4 years. Those of us working in this field know many of them living and working and enjoying life 5, 10, 15 and more years. It is worth while, but it is not a really satisfactory treatment, as is the case of P–32 in patients with polycythemia vera.

To pass on, this is a scanner developed by my associates Tobias and Anger and can be compared to a television scanner (exhibit 8, p. 19). It records gamma rays, from the patient, rather than light rays. The patient lies under the scanner, and it moves back and forth over the patient. The amplifying circuit then converts the energy to light, and a polaroid camera photographs the radioactivity in the body.

CASES	AV. AGE	MED.	SURVIVAL - 3	YEAR 5
129	55	5.4	80%	54
152	41	3.2	54%	20

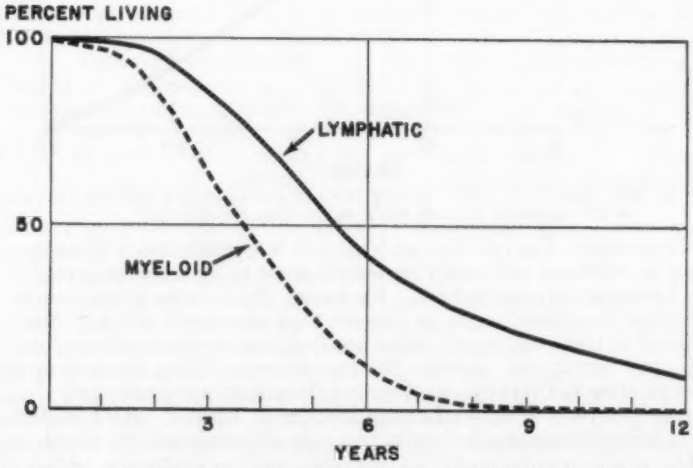

EXHIBIT 7.—Life expectancy from date of onset in 129 patients with chronic lymphatic leukemia and 152 patients with chronic myelogenous leukemia treated with radioactive phosphorus.

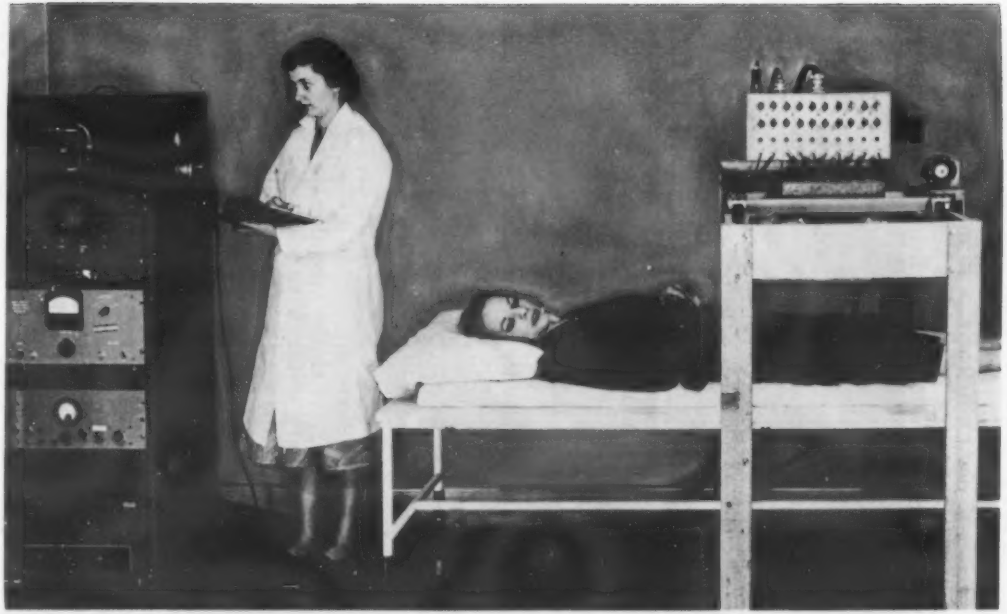

EXHIBIT 8.—The scanner, an instrument which measures the uptake of a gamma-emitting compound over the body and transforms the energy into light so that the uptake can be presented photographically. A medical application of this instrument is the locating of metastatic cancers arising from a primary thyroid tissue cancer in cases where the secondary cancers take up radioiodine in a manner similar to thyroid tissue.

The chart shows such a picture in a patient with thyroid cancer (exhibit 9, p. 21) which has spread to several bony areas of the body. The first picture, the second picture and the third picture are at various times after injection of 5 millicuries of radioactive iodine. This is the 48-hour picture showing those areas in bone where gamma rays are being emitted and photographed. These areas are the sites of the spread of this cancer of the thyroid gland to bone.

It is of interest to point out that this is an example of what Dr. Warren referred to—a man of 75 who has been and is being treated successfully with radioactive iodine, and living a quite comfortable life even though he has this cancer which has been controlled by radioactive iodine.

Representative HINSHAW. Let me get one thing straight. Just because a man has a cancerous condition of the thyroid, which is a gland in the neck, as I understand it, does the spread of that particular cancer, throughout the body, or in various portions of the body become indicated by phosphorus or iodine concentrating in those particular cancers? In other words, is the material in which they concentrate the same as the original material in the thyroid?

Dr. LAWRENCE. Not always. In perhaps 15 percent of the cases radioactive iodine will be picked up. I show this as a pioneering experiment by my colleagues in developing a method to locate cancer in the body. But the problem is to find radioactive materials which will go to all cancers, or to all cancers of one type.

Representative HINSHAW. Let us suppose the gland were some other gland—the gallbladder.

Dr. LAWRENCE. The gallbladder or the pancreas or the ovaries.

Representative HINSHAW. Yes. Would the extension of pancreatic cancer absorb the same material as the pancreas itself?

Dr. LAWRENCE. Not always, no. Some cancers take on functions of the tissues from which they are derived. But by and large they are exceptions.

There are other examples such as cancer of the breast, cancer of the prostate, and cancer of the thyroid.

Representative HINSHAW. With the exception of the latter, those cancers of the genitourinary system have something to do with the procreative system of life, and they would naturally be associated.

Dr. LAWRENCE. But unfortunately this technique has no widespread application at the present time.

Representative HINSHAW. Is it just merely a matter that you know, or is it apparent through a roentgenogram or something of that sort, it can be seen on the photographic plate?

Dr. LAWRENCE. No. In this instance three of these areas cannot be seen in the roentgenogram. We know the spread is there from the scanner but the X-rays don't show it. This may become an important new method for the detection of cancer, and for numerous other investigations.

Representative HINSHAW. I see.

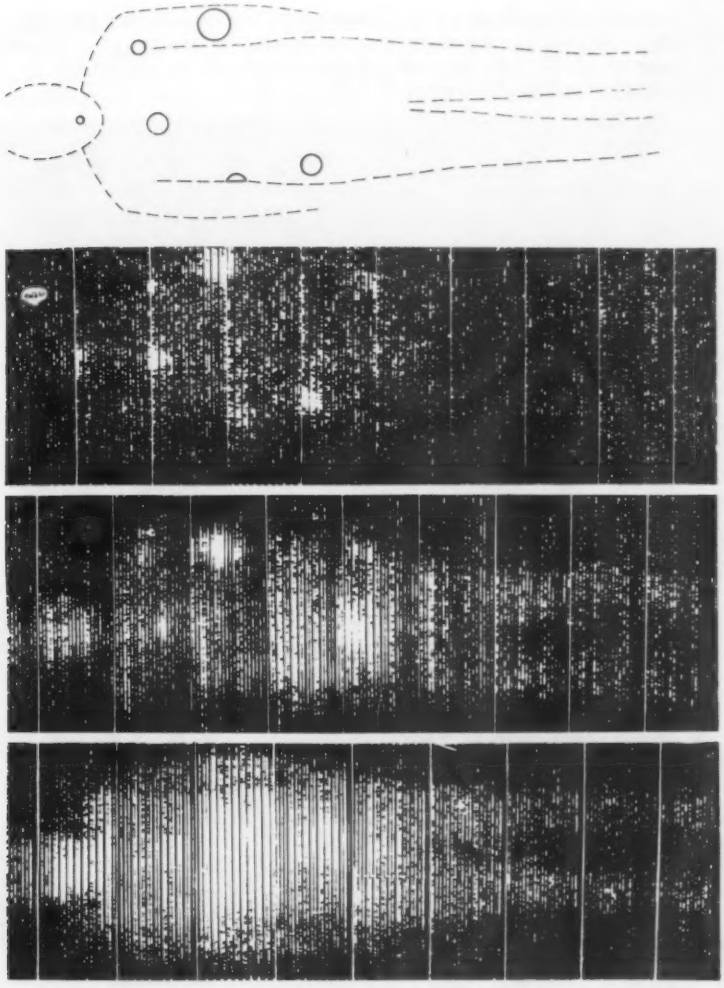

EXHIBIT 9.—Photographs made using the scanner at various times after injection of a tracer dose of radioiodine. In this case a cancer of the thyroid gland had spread to several areas of the bone. After 48 hours (last photograph) the radioiodine is largely localized in the cancer areas, and the malignant areas can be pinpointed. It was impossible to locate three of these areas by X-rays. Since the radioiodine localizes in the malignant tissue of this kind, a larger therapeutic dose of radioiodine can be used to irradiate the cancers selectively within the cancer tissue itself.

Dr. LAWRENCE. Now we will pass on to the next chart (exhibit 10, below). This is a piece of equipment developed because of radioactive hydrogen, which, in the newspapers you read, is important in the development of the hydrogen bomb.

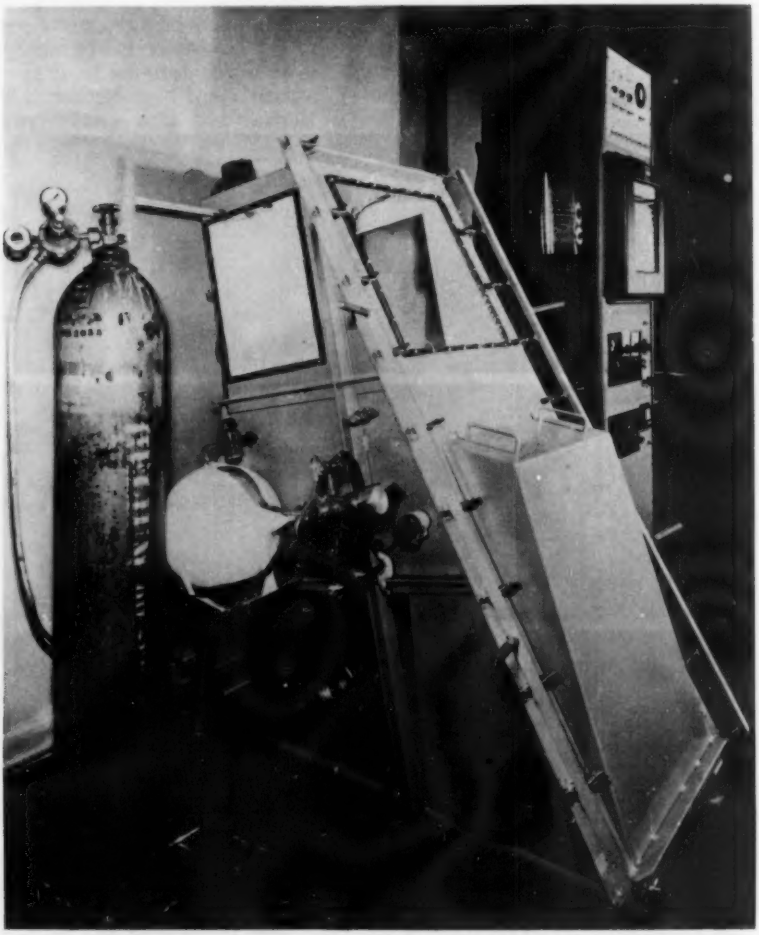

EXHIBIT 10.—Apparatus for measuring body volume. The body volume is measured by the amount of helium displaced by the subject's body. This measurement together with the data obtained of the subject's total body water as measured using tritium (radioactive hydrogen–3) enables the investigator to learn the relative proportions of body water to body fat. Such data are useful in the study of the aging processes and medical problems such as certain heart and kidney disorders where water balance is disturbed.

Representative HINSHAW. Which is this?

Dr. LAWRENCE. This is tritium. This equipment was developed by Siri, one of my colleagues, for the measurement of body volume. A subject is placed in this box, a standard amount of helium is

injected, and the amount of helium displaced enables him to calculate the body volume. It is important to know the body volume, and this is the best method now available for its determination, if you are studying body fat and body water. You can determine with 1 cubic centimeter of tritiated water injected into a normal person or in a patient, taking a blood sample an hour later, the total body water in the body.

We find widespread usefulness of this in the case of people who have water problems. But it also is important in the study of the aging process, because in that process the body water goes down and the body fat goes up. We now have simple and accurate methods for determining body water, body fat, and lean body mass.

Representative HINSHAW. Are you speaking of that well-known subject of geriatrics?

Dr. LAWRENCE. Yes, sir. That is correct.

Representative HINSHAW. I am very much interested in that subject.

Dr. LAWRENCE. We all are. One other application of labeled hydrogen, or tritium, to a problem we are all interested in—in this case using radioactive hydrogen, or tritium for following hydrogen an element common to carbohydrates, proteins, and fats, in the study of cholesterol metabolism: In this case a normal patient, on the left, is fed a meal of fat containing tritiated cholesterol. We all eat cholesterol in our food, and also we make it in our bodies.

Representative HINSHAW. Let's get that straight.

Tritiated cholesterol is hydrogen–3 cholesterol.

Dr. LAWRENCE. Tritium—or hydrogen–3—has to be incorporated into the cholesterol molecule, this fatty or steroid compound.

Representative HINSHAW. The "tritiated" means hydrogen–3.

Dr. LAWRENCE. Correct.

Representative HINSHAW. All right.

Dr. LAWRENCE. In this case here we have a normal man on the left and a man with clinical arteriosclerosis on the right (exhibits 11 and 12, p. 24). This shows the free cholesterol curve being higher on the left and lower on the right. This is a consistent finding in comparisons between normal subject and subjects with arteriosclerosis. The hope is that this type of test may lead to the early diagnosis of a tendency towards arteriosclerosis. Combined with other data obtained from the ultracentrifuge, someone some day will be able to correct this abnormality, which abnormality is present in so many of us after the age of 40 or 45.

Representative HINSHAW. But you have found that to be a fairly constant measure of the presence of arteriosclerosis?

Dr. LAWRENCE. This is a characteristic picture in all normal and pathologic humans studied so far by my associates, Biggs and Gofman. It is also a characteristic of a disease called xanthomatosis, which is associated with severe arteriosclerosis.

There are great hopes that this is going to be a valuable step toward the understanding and eventual solution of this problem.

Representative HINSHAW. You are referring to hardening of the arteries, I take it.

Dr. LAWRENCE. Exactly. Yes, sir.

Representative HINSHAW. And you will be able to learn that whether or not you can see it and measure it otherwise?

Dr. LAWRENCE. That is certainly the hope of my colleagues and myself.

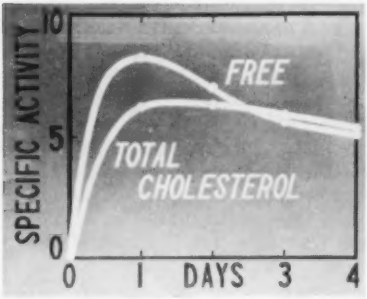

EXHIBIT 11.—Free and total labeled cholesterol in the blood of a normal subject at various times after feeding with tritium-labeled cholesterol.

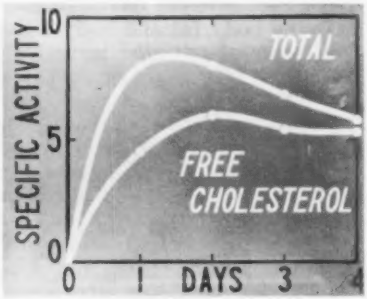

EXHIBIT 12.—Free and total cholesterol in the blood of a patient with arteriosclerotic disease at various times after feeding with tritium-labeled cholesterol. This abnormal pattern is valuable in the detection of arteriosclerosis and also in fundamental research into the interrelationships of fat metabolism and atherosclerosis.

The final chart concerns the cyclotron again. This is the 184-inch cyclotron which was built by the Rockefeller Foundation and the Manhattan District and the Atomic Energy Commission. It was started before World War II, produced the first usable amounts of U-235, but medically it has a unique beam, which is different from the gamma rays from cobalt or X-rays in that it remains discrete and well delineated when it goes into the tissues.

This is a photograph (exhibit 13, p. 25) of the skull of a rat. This white spot is the beam coming from the cyclotron, entering the temporal region of the rat, hitting the rat's pituitary. My colleagues, Tobias, et al., have been able to remove the pituitary in a growing rat in this way.

Here are three litter mates. This rat's pituitary has been removed surgically; this one, by this radiation beam; and this is the normal litter mate. The first two have become dwarfs.

At the present time, there is great interest in pituitary radiation, and from the standpoint of cancer we are using this beam now in treating dogs with cancer experimentally.

There is no human application at the present time. But there is great interest in the ability to remove a tissue like the pituitary, which is the master gland of the body, which controls all of the other endocrine glands.

There is great interest in this from that standpoint and also from the standpoint of selective irradiation of other tissues. The unique qualities of this beam are its pencil-like nature and its ability to deliver relatively greater doses to the deep tissues and less to the tissues such as the skin where the beam enters the body. This is in

contrast to single-portal X-ray treatment with conventional X-ray therapy machines, where the skin dose may be much greater than the depth dose.

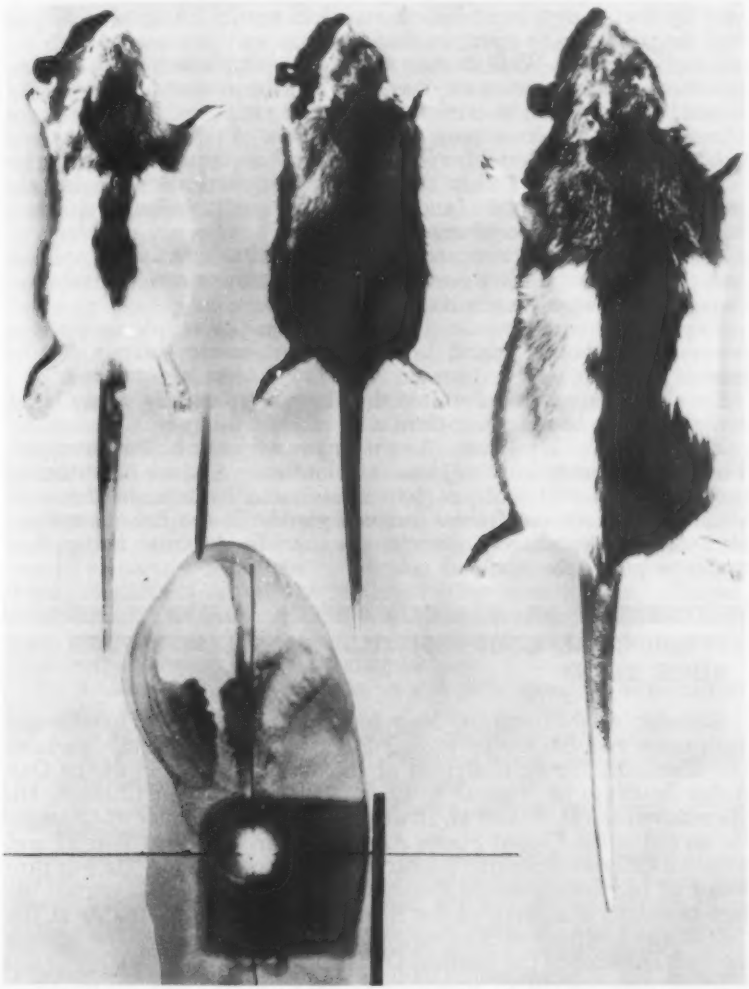

EXHIBIT 13.—Lower X-ray photograph showing how irradiation from the 184-inch cyclotron can be pinpointed at the site of the pituitary gland in a rat without damage to surrounding tissue. Upper left: Three litter mates—the rat at the right has received no irradiation and is of normal size; the pituitary gland of the next has been destroyed by irradiation; the pituitary of the third rat has been removed surgically. Since the pituitary gland controls growth, the effect of removing the gland by either irradiation or surgery can be observed in the slowed growth rate of experimental animals.

Representative HINSHAW. Now, I am greatly interested in that subject, particularly because one who is very close to me is suffering from, I believe, some calcification or deactivation of the pituitary gland. And you have successfully removed, almost excised, the pituitary by that means, by radiation, in other words. And what do you find the results to be upon the rat?

Dr. LAWRENCE. Well in rats that have complete removal of the pituitary, and in humans too, it is known at the present time relatively normal functions can be carried on if they are supplied a small amount of cortisone and in some cases a small amount of thyroid. This could not have been considered for long-term work in animals or man prior to the cortisone era, and in this country surgeons are removing the pituitary completely now, and patients are getting along quite well with small doses of cortisone daily.

It would be a long story to describe the effects, but these animals and patients that I have seen in many ways approach normal even though they haven't a pituitary.

Representative HINSHAW. In other words, the supplement of the hormone of another gland is able to compensate entirely for its removal?

Dr. LAWRENCE. Yes, I think that is true, partially true. That certainly is the hope in long-term studies.

Representative HINSHAW. We thank you very much, Dr. Lawrence. This has been very exciting, this information. And we hope that in the future you will continue your studies and learn more and more about the functions of these various glands in the human system. Because it is exceedingly important to the life of human beings that we learn more about them.

STATEMENT OF DR. MARSHALL BRUCER, CHAIRMAN, MEDICAL DIVISION, OAK RIDGE INSTITUTE OF NUCLEAR STUDIES, OAK RIDGE, TENN.

Representative HINSHAW. Now, for "the development of teletherapy equipment and the use of radiogold in cancer treatment," we have Dr. Marshall Brucer, chairman of the Medical Division of the Oak Ridge Institute of Nuclear Studies. He was born in Chicago, Ill. He received the M. S. and M. D. degrees at the University of Chicago. He served in the United States Air Force during World War II and with the Office of Scientific Research and Development. He was professor of physiology at the University of Texas—medical branch before becoming chairman of the Board of Medical Consultants at the Oak Ridge Institute of Nuclear Studies in 1948. In 1949 he became the first Director of the Medical Division.

Dr. Brucer has put an amazing amount of energy into his program of exploiting the close physical relationship of his institution to the Oak Ridge National Laboratory and into the development of teletherapy equipment based on radioisotopes obtained either as fission products or made in atomic reactors.

Dr. Marshall Brucer, we are delighted to have you here to present to us the facts at your command.

Dr. BRUCER. Mr. Chairman, the current program of the ORINS Medical Division is directed toward the application of radioactive

isotopes in the study of the treatment and diagnosis of cancer and allied diseases. The Medical Division maintains a 30-bed hospital. With its own laboratories and those of the closely associated Oak Ridge National Laboratory, it is equipped to investigate all phases of the problems of the use of radioactive isotopes in man. Since most of the isotopes are new and untried as drugs these problems have ranged from the purification of raw materials, through their irradiation in various reactors and cyclotrons, their chemical and radiation toxicity, their metabolic behavior in animals, clinical testing in human patients, and finally to a clinical trial in either diagnosis or therapy of a specific isotope preparation in a specific disease. There is also a continuing routine use of well-established isotopes but only as a part of the clinical training of staff and visiting physicians. The program is designed to be broad in scope rather than to concentrate on any specific clinical problem. It emphasizes the study of the use of isotopes rather than the study of cancer. It recognizes a responsibility to develop materials and methods that are adaptable to organizations unable to duplicate the facilities of the Atomic Energy Commission.

The reasons for selecting an item for study in the Medical Division are diverse. Selection depends upon the interests and training of the permanent and visiting staff and of selected consultants from about 30 associated medical schools. A program item may be selected by the staff because of a good lead developed in another laboratory which does not have available the facilities of the AEC. The availability of patients and the results of previous studies often dictate the necessity for further studies. Some studies have been started because of the results of basic work in the production facilities of AEC plants and some are started to check the results of other investigators. There is a continuing search through the table of isotopes for new possibilities.

In the continuous process of revising the program there is always an attempt to balance the following factors:

1. Basic clinical investigation and developmental clinical testing.
2. Studies in animals and studies on human patients.
3. The use of internally administered isotopes and the external application of radiation from isotopes.
4. The development of well-known isotopes and trials of new isotopes.

In addition to major program items there is always present an opportunity to follow minor and short-range projects which are presented by the nature of the material already under study. Since human life is at stake in all of the clinical work, the experiments cannot be conducted only as studies of biological reactions to a drug. The human experiments must always be subordinated to the necessity for administering the best possible medical care to each patient. In the human phase of each problem it is invariably true that more time and expense go into the care of the patient than into the study of the isotope. Although many patients receive a direct benefit from the use of various radioisotopes, complete success is seldom achieved. A detailed study of failures in treatment is therefore a necessary part of the program; this is of sufficient importance that a portion of the patients are accepted without hope of success. The final experiment

in any drug problem must be carried out in the human being and animal studies are inconclusive. When such studies are done with potentially lethal drugs such as radioisotopes only terminal patients may be used. In such studies the only benefit the Medical Division can offer a patient in repayment for his confidence is good nursing care and humane palliative treatment. Such a program is a necessary expense in the study of a new isotope.

The Medical Division program is completely devoted to research and teaching. It has no service function in the community and does not accept patients because the treatment is unavailable elsewhere. However, the staff realizes its obligation to make immediately available to the medical profession any of the results of its experience. Therefore, there is an active program devoted to the training of practicing physicians and consultation with the medical profession. Further, in many fields, especially those which closely mimic the historical use of radium and X-ray, there are few facts and many diverse opinions. To reconcile these diverse opinions, the staff has gathered a large body of consultants to help in guiding the major items of concentrated effort.

I will present to you today only a few examples of some of the more important problems that have been studied.

The Medical Division at Oak Ridge was placed in Oak Ridge to take advantage of the facilities of the world's largest producers of radioactive isotopes. Hence, our work has emphasized the study of radioactive isotopes in the treatment of certain diseases, particularly cancer.

We have three primary problems. First of all, it is necessary to find out which isotopes are successful in the treatment of disease. But since this implies that we have patients with large amounts of many radioactive isotopes in their bodies, we also have the additional job of finding out what happens to these isotopes, because in many cases they are of elements that are very little known and have been very little studied in the human or animal body.

Representative HINSHAW. You say that you have patients with many of these radioactive isotopes in their system. You must mean that they are exposed to radiation, as employees of Oak Ridge.

Dr. BRUCER. No. Fortunately not. This doesn't occur in the laboratories I have visited. However, we do have patients who are given isotopes to attempt to treat or to diagnose certain kinds of disease. Occasionally we give one isotope. Occasionally we give 2 and as many as 3 isotopes to 1 patient.

Representative HINSHAW. Then you directly treat the patient?

Dr. BRUCER. We attempt to directly treat the patient, but seldom with complete success and hence we also have another responsibility. Beside studying the action of these isotopes in the patients, since we often fail in the treatment, we have the responsibility for trying to find out why we fail.

Further, when there is found a method for treating patients with radioactive isotopes, this is relatively worthless if we are the only ones that can do the treatment, or if the National Laboratories connected with the Atomic Energy Commission have the only facilities for giving the treatment.

So we have the further responsibility for training physicians and for making available to the general medical public the results of our

investigations and those of other laboratories connected with the Commission.

Before we can give an isotope to a human being, especially if it is an isotope of a relatively unknown and rare element, we must do considerable testing in animals. Figure 1 (exhibit 14, p. 30) shows one of the animal research laboratories, in which a large part of our preliminary work is done. I will show, in figure 2, a picture of a potentially useful new isotope. It was found by a number of scientists in Switzerland and in America that colloidal suspensions of certain elements, when injected directly into a tissue, would stay put where they were put. If this were true, then, by using a radioactive colloid, we could effectively and selectively irradiate any small area of the body. Further, if the colloid were placed in the lymphatic drainage of a cancer, the radioactivity would be picked up by the lymphatic system and would be carried along the same channels that the spreading cancer follows.

The radioactive gold colloid does not do this very well, and so many other isotopes are being tried. Figure 2 (exhibit 15, p. 31) is a picture of the spread of a solution of yttrium chloride, which has been injected into the pelvic organs of the dog. The isotope was injected around the uterus and you can see that it has spread through the tissues immediately surrounding the uterus, just as cancer of the uterus would spread in a human being. Then it also is carried along the lymphatic channels just as a metastatic cancer of the uterus would be carried. If such an experiment can be repeated successfully many times, it might be worth while in a few years to try such a method in treating metastatic cancer of the uterus. If this element does not work well in the human being, then there is another, an isotope of lutecium, that can be tried.

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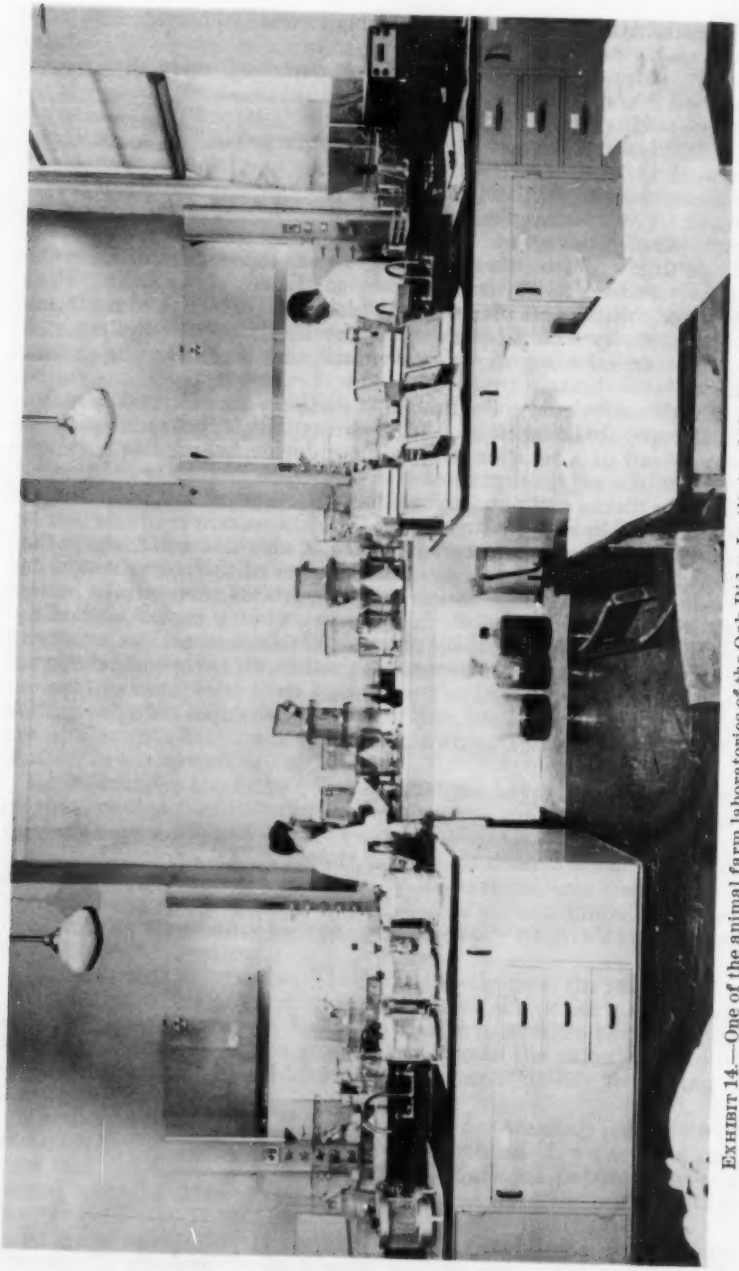


EXHIBIT 14.—One of the animal farm laboratories of the Oak Ridge Institute of Nuclear Studies, Medical Division.

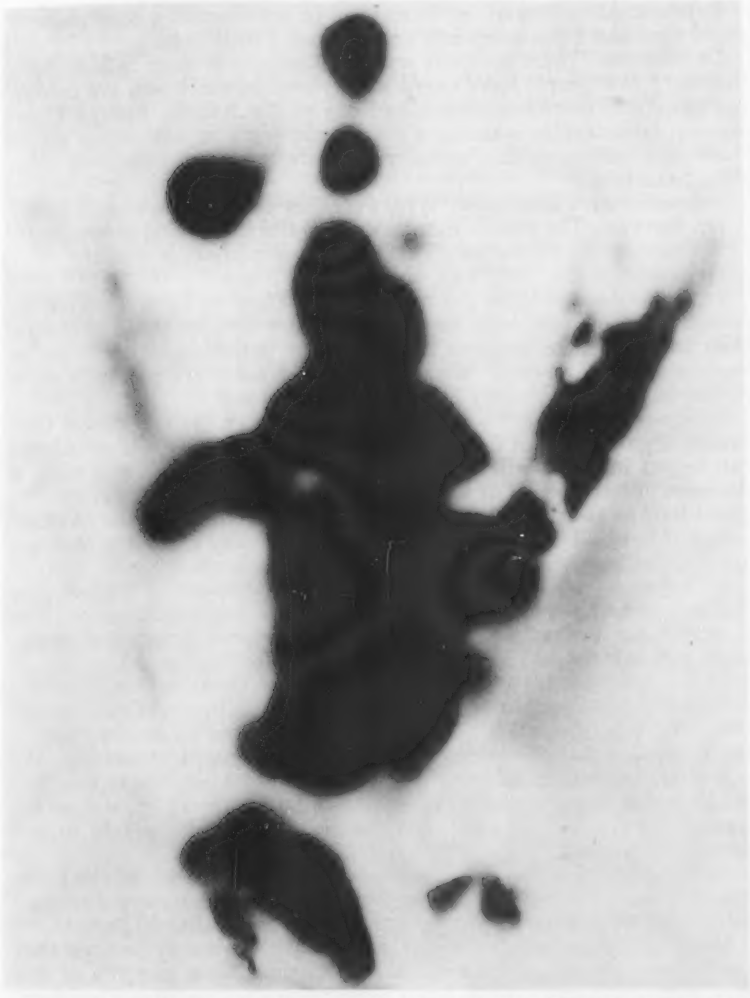


EXHIBIT 15.—Gross autoradiogram 3370 (dog 420295). Part of a distribution study of interstitial yttrium injected into dogs. Interstitial injection of approximately 2 mg of yttrium traced by approximately 250 microcuries of Y 91 into the lower uterine segment 7 days prior to sacrifice. The soft tissue of the pelvis and the iliac structures, aorta and para-aortic tissues, kidneys and adrenals were exposed to film for orientation purposes as a guide to sampling for radioassay. The yttrium is retained at the site of injection but also has diffused along the adventitial tissues and has been carried to iliac and para-aortic lymph nodes.

Representative HINSHAW. Doctor, I am sorry. My chemistry stopped before that element was discovered. What is it again?

Dr. BRUCER. Lutecium is the last element in the first series of rare earths.

Representative HINSHAW. It was not in my chemistry book some 30 years ago, and I am sorry but I never heard of it before.

Dr. BRUCER. There are quite a few elements now being talked about that very few people have heard about, but some of these are becoming more and more important, and one of the Atomic Energy Commission laboratories is doing a very great work in separating all of these rare earths, so that actually they are becoming relatively common materials.

Representative HINSHAW. Where do they come in the atomic scale?

Dr. BRUCER. The atomic numbers are in the sixties and seventies.

Representative HINSHAW. That is beyond calcium, is it not?

Dr. BRUCER. Oh, yes; way up beyond calcium.

In figure 3 we go on to the next phase. After we have tried out an isotope in the animal sufficient to the point where we think it is safe, then we give these isotopes to the human patient and try them in various types of disease. We select these diseases very carefully since no one isotope can be used in every type of cancer.

In figure 3 (exhibit 16, p. 33) the patient has a type of cancer that causes large volumes of fluid to leak into the chest cavity. If an isotope can be put into and will stay in the chest cavity, then it will cause a decrease in the amount of fluid that is formed in the chest cavity. In about half of the patients, the treatment works to reduce the accumulation of fluid. The patients are not cured of their cancer, but they are allowed to live just a little bit longer and in relative comfort.

In figure 4 (exhibit 17, p. 34) you will see that before we can give the isotope to the patient, first of all we must prepare the isotope as a drug. As you can see, this takes a considerable amount of equipment which is not ordinarily found in a hospital pharmacy.

In figure 5 (exhibit 18, p. 35) there is shown the distribution of the gold that has been given to one of these patients with an effusion in the chest. This is the same kind of a scintogram, scanning technique, that Dr. Lawrence described, using a somewhat different instrument. We can see that superimposed on the background radiation, the radioactive gold has distributed itself throughout the fluid in the chest, and we are irradiating the surface of the thoracic cavity very effectively in this particular patient.

As I said, such a treatment works in about 50 percent of the cases. We still have the responsibility, and I think our primary responsibility now, to find out why it does not work in the other 50 percent.

Many of the patients we select are selected purposely because they are terminal patients. We know that they will die in spite of any treatment. Usually we can learn more from such patients than from the successes. One of the ways of learning new facts is shown in figure 6 (exhibit 19, p. 36) in the autoradiographic techniques thin slices of organs are placed on a photographic film, the radioactivity exposes the film, and we get a picture of the distribution of the radioactive isotope in this particular organ.

In figure 7 (exhibit 20, p. 37) we see what has happened when radioactive gold was given intravenously in order to irradiate a metastatic cancer to the liver. This, again, is one of the failures in treatment. The two upper photographs show a thin slice of liver; you can see the whitish metastatic tumor inside of the dark normal liver. In the lower picture is an exposed photographic film. You don't see the tissue here. All you are seeing is the photograph of where the radiation was

in the piece of liver. The picture shows that we were able to distribute the radioactivity completely in all of the normal tissue, but we were not able to get it into the tumor itself. This is one of the reasons why this kind of therapy has been a failure. In very small tumors we might give adequate crossfire radiation, but for very large tumors we would not be able to treat patients in this way.

However, one other idea was brought up at the University of California, and that is that if we could do a scintogram over the liver we would find holes in the scintogram indicating areas of tumor. Thus, this might be developed as a diagnostic technique.

In figure 8 (exhibit 21, p. 38) we show a different kind of a distribution, with a different isotope. This is an isotope of gallium which tends to deposit in areas of developing bone tumors. The spread of bone sarcomas is invariably to the lung, and in this thin slice of lung you can see all of the round spots that are the tumor metastases which have spread from the primary tumor in the bone.

Alongside the photograph is the autoradiogram, the radiation picture of where the gallium isotope went, and you can see that the gallium in all cases goes exactly to the metastatic tumors but does not go to the normal tissue.

Representative HINSHAW. That second photograph, I take it, is a negative rather than a positive, is it not?

EXHIBIT 16.—Administration of an isotope in a human patient.

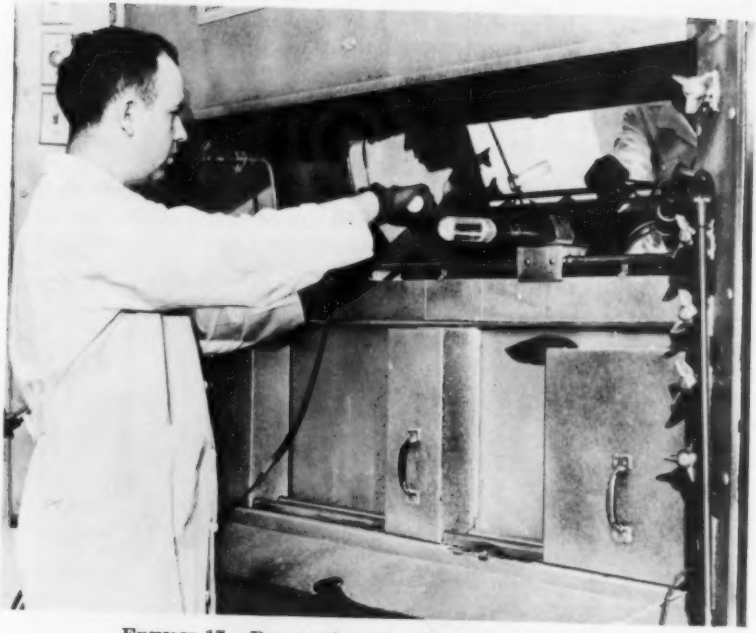


EXHIBIT 17.—Preparation of an isotope for a patient.

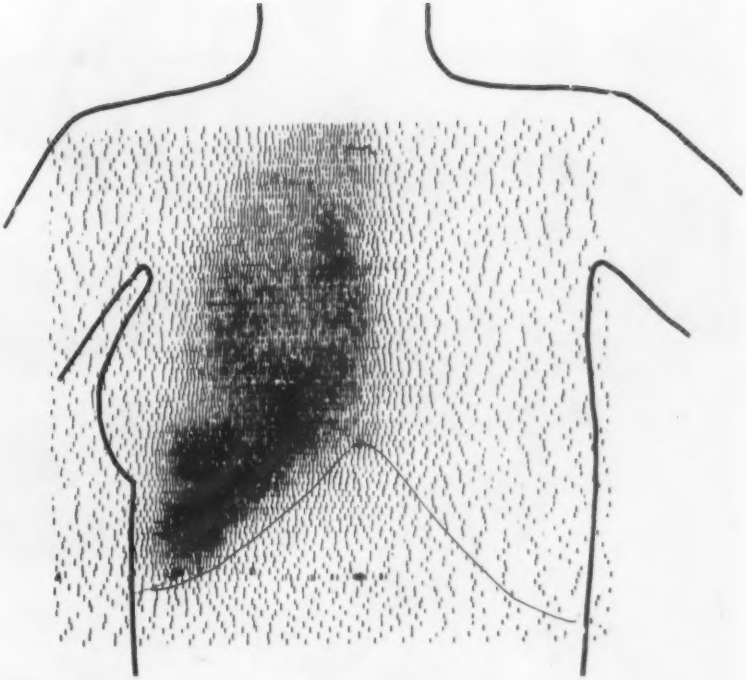


EXHIBIT 18.—Record made by scintiscanner showing the distribution of gold 198 in the chest.

EXHIBIT 19.—Loading an autoradiography cassette.

EXHIBIT 20.—Photograph and autoradiogram of a thin slice of liver from a patient who had been given gold 198.

Dr. BRUCER. That is the negative, yes.

Representative HINSHAW. Because the scintillations are shown in black instead of in white.

Dr. BRUCER. In black. All the black spots are due to the radiation affecting the film.

This particular kind of treatment failed for a different reason than the failure of the gold in the liver cancer. It failed because the energy of this particular isotope is exceedingly high, so that no matter where the chemical is deposited, the absorption of energy is far removed. Also, this kind of cancer is very resistant to radiation. However, there are other isotopes that might be tried, which are low-energy emitters, and there are other cancers that are not so resistant.

With figure 9 (exhibit 22, p. 39) we go on to a different kind of autoradiogram. Whereas in the last two pictures we showed the distribution of the isotope grossly throughout the entire organ, this is a picture enlarged a thousand times and shows the miscroscopic distribution of the radioactivity that was given to the liver.

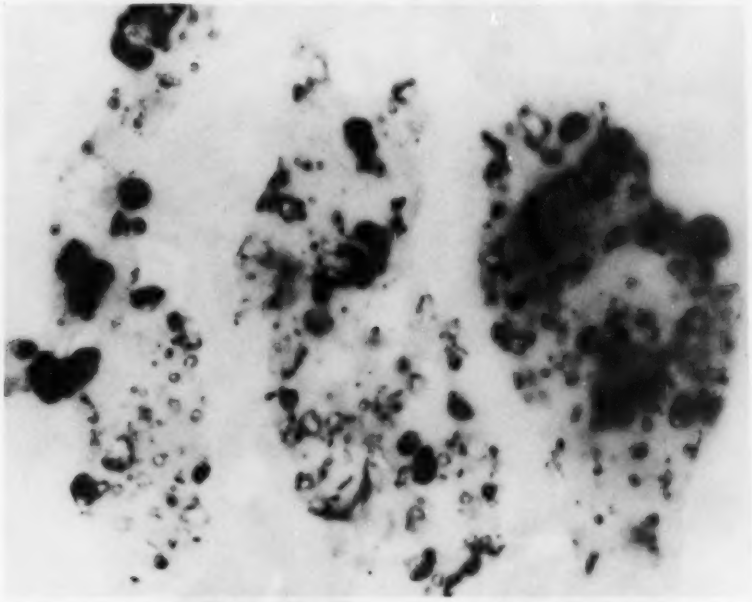


EXHIBIT 21.—Photograph and autoradiogram of a thin slice of lung from a patient who had been given gallium 72.

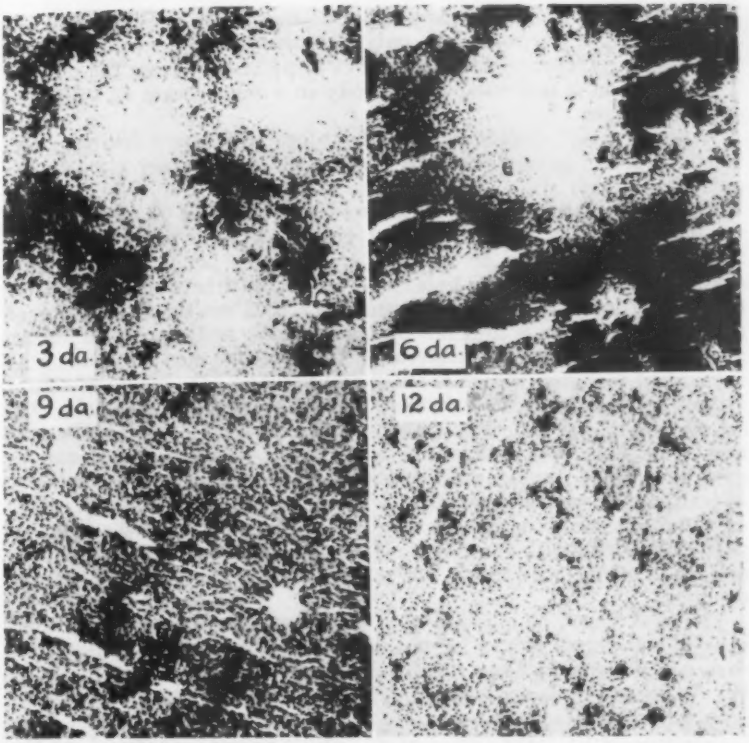


EXHIBIT 22.—Microscopic autoradiogram of liver tissue showing the distribution of the radioactive gold 198.

In figure 10 (exhibit 23, p. 41) we go to a somewhat different kind of usefulness for isotopes. Rather than internal administration of the isotope to irradiate the tumor from the inside out, we now speak of a source of radiation on the outside and aimed as a beam through the body. This mimics the old X-ray machine, which has been used now for about 60 years. However, we think we can do the same job a little bit better with isotopes than can be done with electrical generators.

In almost any of the units that you will see, and you will see quite a few of them being described during the next few days, the problem is always the same. Instead of having a very large electrical generator of X-rays, we have a very small source of radioactivity. This source is surrounded by a pot of lead with a hole in it, and there is some gadget devised to turn the beam of gamma rays on and off. These are called teletherapy machines, and they have been developed primarily to treat cancer.

Representative HINSHAW. Just a moment. I think that you should define this term "teletherapy," because it is a new term so far as the general public is concerned, certainly, and it is worthy of some attention.

Dr. BRUCER. It is a therapy machine because it is being used not for diagnostic purposes but only for therapeutic purpose. It is "tele"-therapy, because the machine is at a distance from the patient. The radiation is delivered to the body in a small beam and directed at a tumor area.

Later on I will distinguish this from brachytherapy devices. The word "brachy" is used, because we put the source very close to the patient.

Figure 11 (exhibit 24, p. 42) shows the first cobalt 60 machine that we developed for the purpose of getting a high energy beam of radiation which could be directed at a tumor. It is nothing more than a pot of lead with a hole in it, except in this case it is a pot of tungsten alloy. But you will remember that we think that one of our responsibilities is to make things available to the medical public, and not just to develop something that we can use ourselves. At the cost of tungsten, which is about $20 a pound (the machine weighs almost a ton), we have not made this machine very available. On the next machine, figure 12 (exhibit 25, p. 43), we have tried to take this same idea and make something that is practical and can be used by a large number of physicians. The machine is a small pot of lead, which weighs only about a thousand pounds. It has a source of radiation, which turns on and off and delivers the same beam of million-volt gamma rays that the bigger machines deliver. The next picture, figure 13 (exhibit 26, p. 44), shows a full view of the machine.

The first cobalt 60 machine that was developed as a piece of commercial equipment is now being sold for about $80,000. In the latest design, the cost may come down to around 20 to 25 thousand dollars. We feel that this is an important step toward making cobalt 60 economically available to the medical public.

Representative HINSHAW. Let me ask whether you feel that the radiations from this machine will in anywise supplant the so-called medical reactor or experimental-type reactor that is being produced by one of the companies on the west coast.

Dr. BRUCER. This type of machine produces only gamma rays. It will probably partially supplant the electrical X-ray generators. However, the medical reactor produces something more than gamma rays. In addition to the high energy which it produces, it also yields a neutron beam which has many uses. Dr. Farr is going to talk about this later. We cannot produce neutrons with teletherapy machines.

Representative HINSHAW. I understand that it does do a part of the work of the so-called medical reactor.

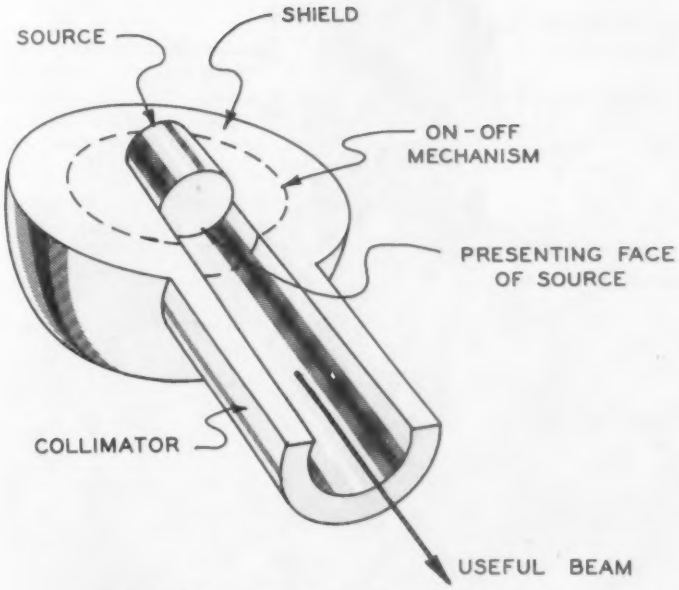


EXHIBIT 23.—Basic design of any unisource teletherapy unit.

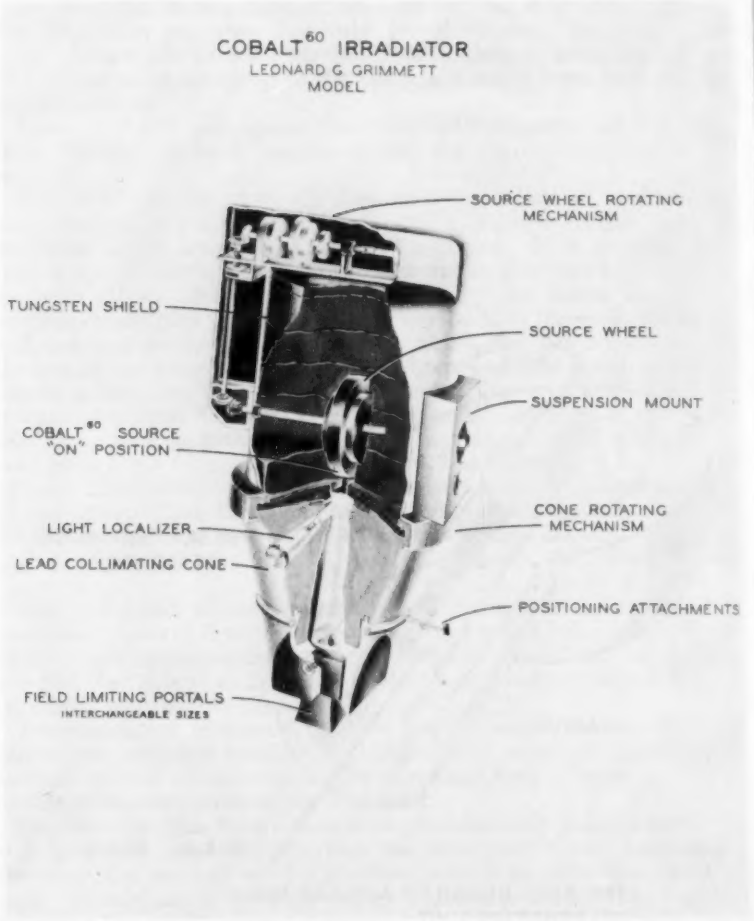


EXHIBIT 24.—Kilocurie cobalt 60 unit. A teletherapy unit designed to contain over a thousand curies of cobalt 60.

Dr. BRUCER. It does a small part of the work that a reactor could be made to do.

These are the simple machines that I have just shown you in figure 14 (exhibit 27, p. 45). Figure 15 (exhibit 28, p. 46) shows a much more complicated machine. The previous machines are using cobalt 60, which has a 5-year half life. The source of activity decays at the rate of 1 percent per month. It would be more useful if we had an isotope that decayed much more slowly, and there is such an isotope, cesium 137. That isotope has a slightly lower energy, which means that the protection problem is not quite so great. Therefore, we could use a lighter weight device, and instead of just having one beam pointed toward the patient, now we can achieve complete freedom in which the beam is rotated to follow any kind of a pattern

around the patient. This is a prototype model. It is not a practical machine. But from this, we think that such practical machines as will be described tomorrow can be made.

Representative HINSHAW. How does the energy of that machine compare with the standard X-ray?

Dr. BRUCER. This is about equivalent to a million-volt X-ray machine. The cobalt is about equivalent to a 2-million-volt X-ray machine.

Representative HINSHAW. The standard X-ray machine?

Dr. BRUCER. The standard million-volt therapy machine.

Representative HINSHAW. That is right. So it is about standard X-ray machine energy?

Dr. BRUCER. The usual X-ray machine energies are around 250 kilovolts. There are very few million-volt X-ray machines available.

Representative HINSHAW. Oh, I thought you said the standard X-ray machine was a million volts.

Dr. BRUCER. There is a 1-million-volt X-ray machine available, but there are very few of them in operation. They are very costly.

Representative HINSHAW. So this departs from the standard X-ray machine. It is four times the energy, that is.

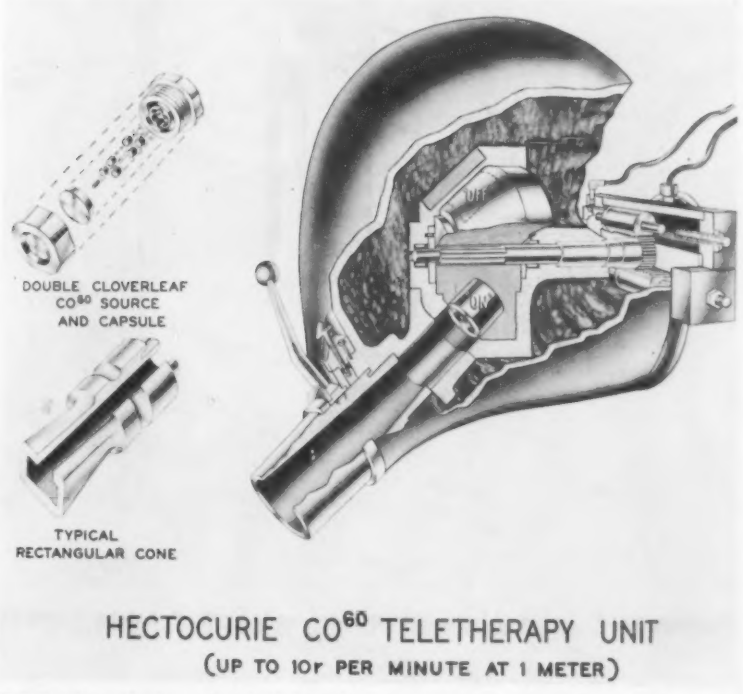


EXHIBIT 25.—Hectocurie cobalt 60 unit. A teletherapy unit designed to contain many hundreds of curies of cobalt 60.

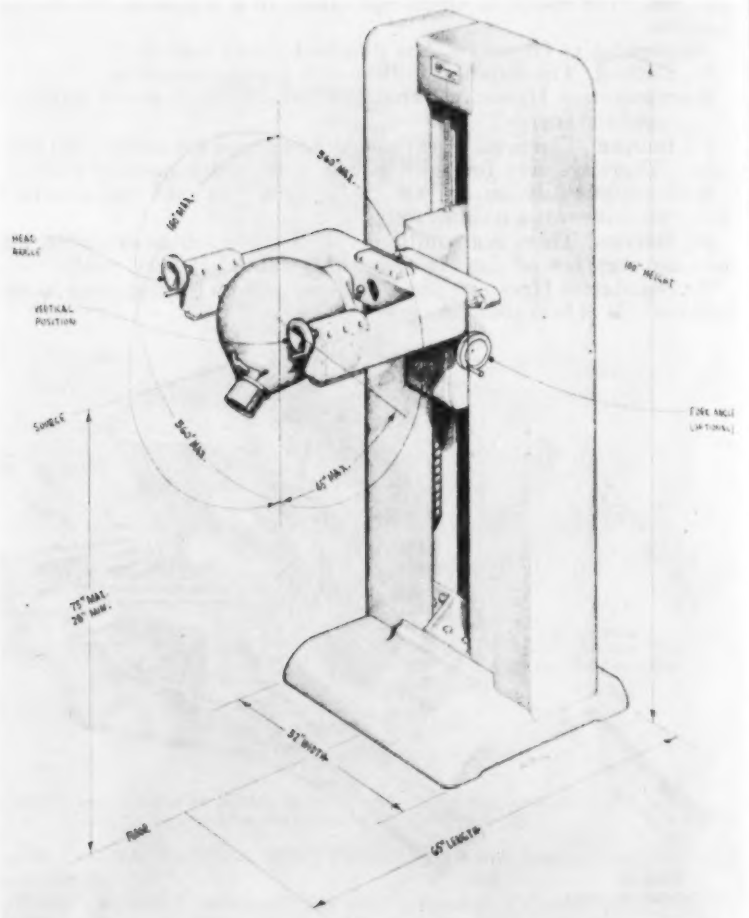


EXHIBIT 26.—Full view of hectocurie machine made by W. F. & John Barnes Co.

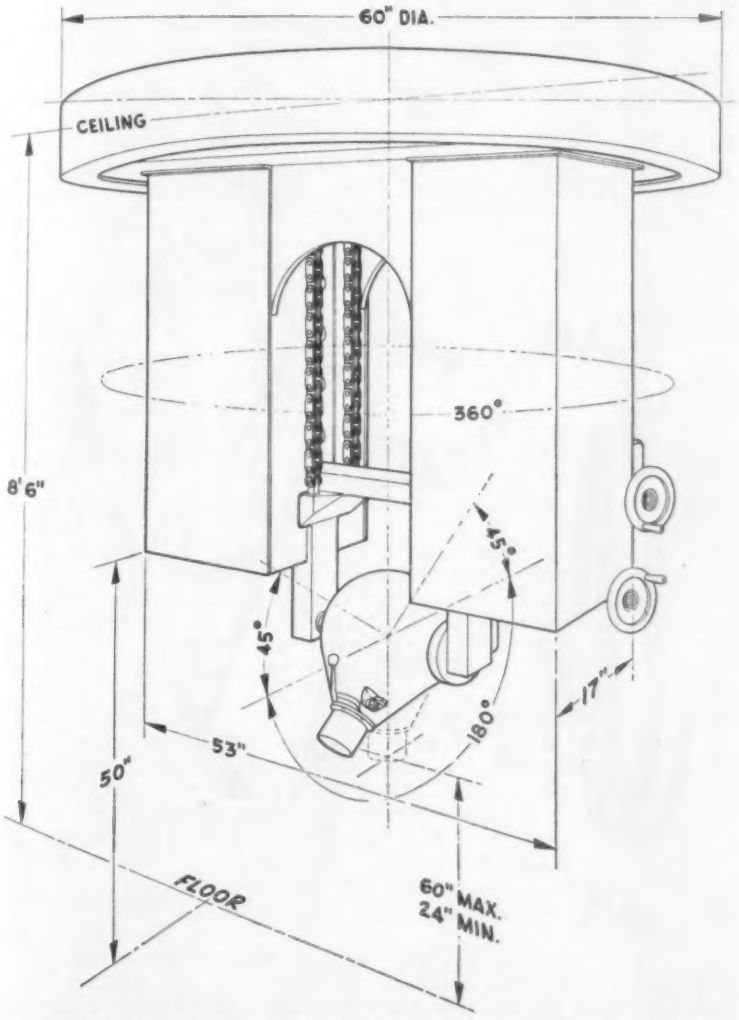


EXHIBIT 27.—Full view of hectocurie machine on a ceiling suspension.

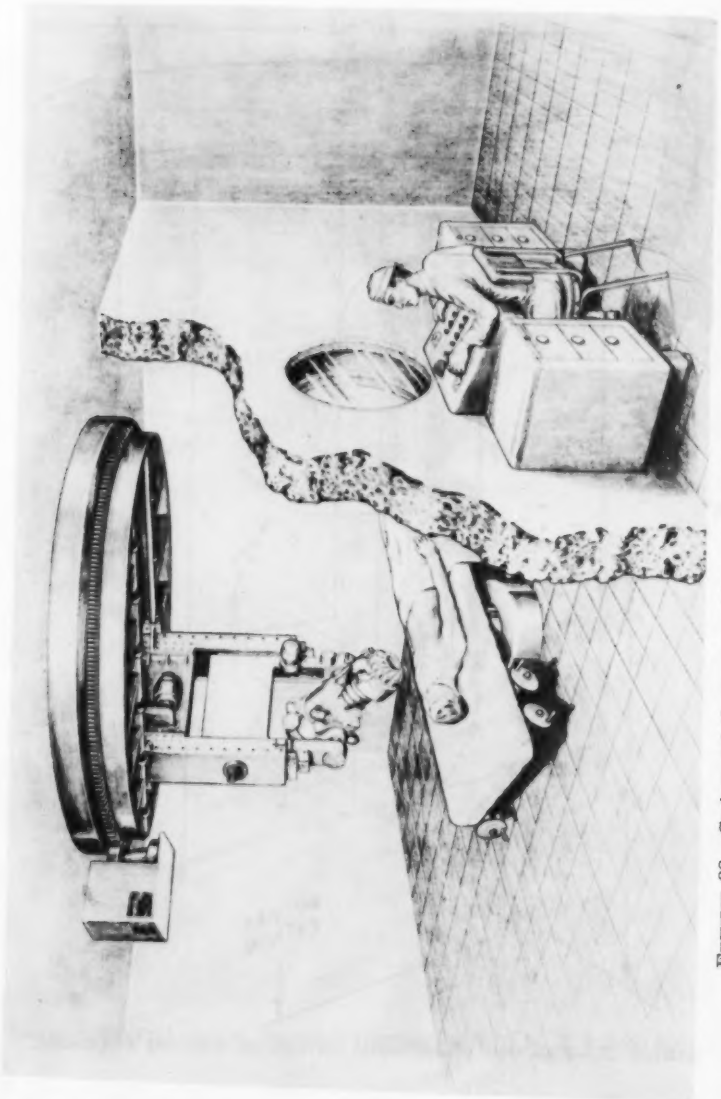


EXHIBIT 28.—Cesium teletherapy machine. A prototype moving field therapy device.

Dr. BRUCER. About that, yes.

Representative HINSHAW. What is the cost of the X-ray machine versus this type of machine?

Dr. BRUCER. The cost of the 250 kvp, the usual X-ray machine, that is being used throughout the country now, is about 15 to 20 thousand dollars. The upkeep in that machine is approximately $5 per treatment.

Representative HINSHAW. I have often wondered why that was so expensive, but you say it is upkeep.

Dr. BRUCER. It is expensive because you have to replace tubes and you must maintain a room, laundry, cleaning, and other operating expenses. The cost of the energy for 1 treatment from 1 of the medium curiage cobalt machines, as shown in the previous photograph, is approximately 12 cents. But this is only the cost of the energy. On top of this you have to put the cost of maintaining a therapy room, which brings it up to something like $2.50 per treatment. One of the big advantages of the radioactive isotopes in this case, for this particular kind of treatment, is purely an economic advantage. We not only are getting a much higher energy, a little better than twice the depth penetration, but we also are producing it cheaper than can be done with the ordinary X-ray equipment.

Representative HINSHAW. Well, now, that is exceedingly interesting, particularly in view of the fact that we as citizens spend large sums of money for X-ray treatments. You say that it can be produced for materially less, approximately one half, for twice the penetration?

Dr. BRUCER. Correct. This is also of interest to the X-ray companies, who feel that this type of machine might very easily supplant the 250 kvp X-ray machine. If it does, however, then the Commission has the responsibility for maintaining a flow of cobalt to supply these machines.

Representative HINSHAW. How much cobalt does it take?

Dr. BRUCER. For this particular machine, it takes approximately 600 curies of activity. For the larger machine, which will be described tomorrow, it takes approximately 2,000 curies.

Representative DURHAM. The cost of that is how much, doctor?

Dr. BRUCER. The cost of the 600 curies, completely packed for use as a therapy source, is between 3 and 4 thousand dollars. The cost of the large source is about $20,000 to $25,000.

Representative DURHAM. And the machine costs how much?

Dr. BRUCER. The cost of the medium curiage machine is now approximately $20,000 to $25,000, depending on how you design the suspension mechanism.

Representative DURHAM. It is patented, I guess.

Dr. BRUCER. On this particular machine, there isn't anything to patent. I don't think there can be a patent on the larger machine because it was designed by Atomic Energy Commission personnel.

Representative DURHAM. That is true.

Dr. BRUCER. On some of the machines I think there are patents, but there are no new principles involved here. This is nothing but a pot of lead with a wheel on the inside to turn it on and off.

Representative HINSHAW. There can be no patents on the source or the application of the energy. There could merely be patents on the device itself, the mechanical part of the procedures.

...therapy machine. A prototype moving field therapy device.

Dr. BRUCER. I don't think I am competent to discuss patent policy.

Representative HINSHAW. I think that we would be interested in receiving from Dr. Bugher some comment concerning patent policy.

Dr. BUGHER. Generally speaking, as Mr. Hinshaw has pointed out, only the devices themselves are patentable. Normally in our unclassified-research program carried on at universities, hospitals, and private-research institutions the patent provision in the contract provides for the Commission to determine rights as between the Government and the institutions. It is the policy of the Commission to accord nonexclusive licenses to applicants upon request. Our intent is to encourage private participation in the program by assuring, within reasonable limits, that scientists may realize a fair return on the fruits of their labors. On the other hand, we feel that no individual or institution should profit unreasonably or exclusively from inventions made possible through the use of public funds.

Representative DURHAM. Since the public has invested so much in the production of the source of energy, whether it is cobalt or cesium, the fact is that all we have done is to produce the material. Of course you could not complete the idea without the machine, and now we find ourselves in the expensive condition of having to carry out something in this way.

Representative HINSHAW. May I ask the doctor if he is able to state the comparative cost of a million-volt X-ray machine?

Dr. BRUCER. A million volt X-ray machine can be installed, I think, for between $70,000 and $90,000.

Representative HINSHAW. Very materially higher than the cost of this machine.

Dr. BRUCER. Yes. So economically we, in using radioactive isotopes, have a big advantage.

Representative DURHAM. I just do not understand why the machines are as expensive as they are.

Dr. BRUCER. I could go into some of the expenses that the companies have put into the design and development of this type of machine. It is a small volume business and the development and testing costs are high.

For the machine shown in figure 15 (exhibit 28, p. 46), which is admittedly a prototype model, the Atomic Energy Commission is paying about $55,000 for its development. A group of 22 universities have contributed approximately $15,000, and then the W. F. & John Barnes Co., who are producing this machine, must have put in about $20,000 of their own money, to develop this particular device.

Representative DURHAM. Well, it is nothing like as complicated as an IBM machine.

Dr. BRUCER. This particular machine is, because a computing mechanism is attached to the machine. The movements of this machine are so complex that they cannot be done by hand. Therefore there is a computing machine attached as a part of the driving mechanism.

Representative DURHAM. That is different, of course. But I am talking just about something to carry out your experiment with radiation. You just put the source in there, and that is all there is to it, except for a very few simple operations.

Dr. BRUCER. For such experiments all we need is a small cobalt machine, which is nothing more than a pot of lead with a hole in it.

Representative DURHAM. That is right.

Dr. BRUCER. There is another factor in the economic picture of the early development of the hectocurie cobalt 60 machine, shown in figure 16 (exhibit 29, p. 50). The first four people to adopt the unit and to put them up in their universities are at Cedars of Lebanon Hospital in California, at Wayne University in Michigan, in the Medical School at the University of Arkansas, and a similar type of machine at Emory University in Atlanta. The owners of these first four units had to pay as much or more to protect the room and to build shielding around the room where this machine was being used than was being spent on the machine itself. Therefore, this problem of area shielding, of which materials can be used and which cannot be used, is an important problem.

In figure 17 (exhibit 30, p. 51) you see one way of measuring the amount of shielding that is necessary in various positions from the cobalt machine. In this case, we are using marble as a shield because it is easy to manipulate and constant in density, but we could use any material.

In figure 18 (exhibit 31, p. 52) you see the results of measurements on a whole series of materials. The series starts with balsa wood (and it would take a tremendous thickness of balsa wood to shield a beam from cobalt 60), and ends with uranium, which would make a very fine shield if you could get that much of it. Any of these materials give an equal amount of protection. The whole problem of devising room shielding to protect personnel is to pick out of this list the type of material which best fits the problem.

Representative DURHAM. Why would they choose any particular material? Just because it is light, or absorbent, or what?

Dr. BRUCER. Figure 18 is a density scale of relative absorption. Actually, it takes so much greater thickness of the "lightest" material to give the same amount of protection that by using the lightest material you would have the heaviest shield. The most economical material to use from the standpoint of weight only would be uranium. But that is not the most economical to use from the standpoint of cost.

Representative HINSHAW. I take it that that chart is plotted on a logarithmic scale?

Dr. BRUCER. It is, yes.

Representative HINSHAW. And if it were extrapolated into an arithmetic scale, it would reach to this ceiling.

Dr. BRUCER. It would reach up to the ceiling; yes.

Representative HINSHAW. Let me ask: On that chart—I can't read the names given to the materials—what is the best and most economical material to be used for shielding?

Dr. BRUCER. The answer to that question becomes an engineering and an architectural problem. Usually the most economical materials to use are the earth-type materials such as concrete, marble, transite, granite, limestone, and dirt. However, the problem now becomes more than one of radiation protection. If you use marble, for example, you need no finish on the wall, but if you use concrete you must usually have a finish. Which is the most expensive? This is some-

thing that also becomes dependent on the area of the country and is largely a local problem.

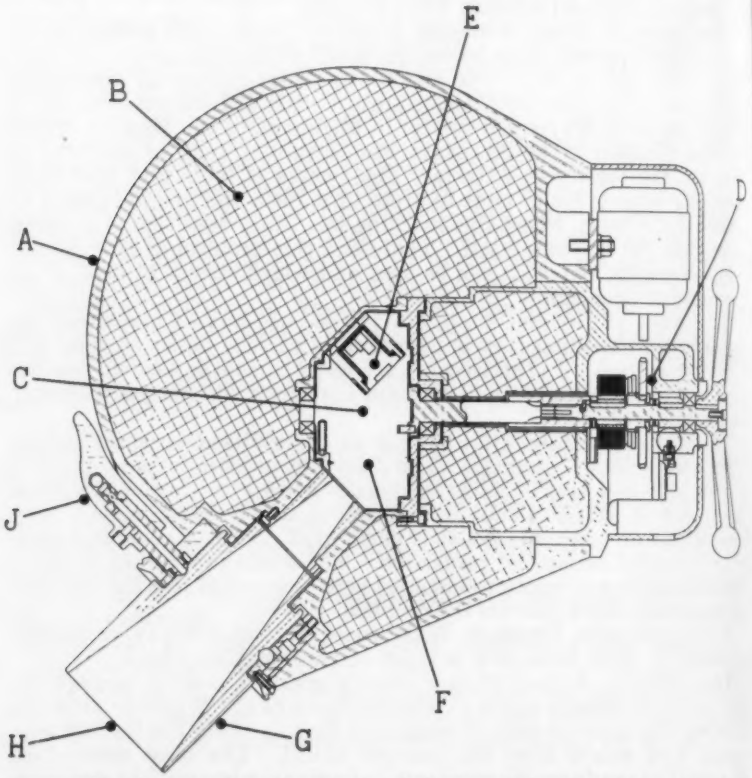


EXHIBIT 29.—Cross section of hectocurie cobalt 60 teletherapy machine. A—steel casing, B—lead primary shield, C—tungsten alloy rotating wheel shutter mechanism, D—automatic shutter control mechanism, E—standard cobalt 60 source capsule in "off" position, F—position of source when "on", G—one of many beam defining cones, H—thin electron filter, J—locking device for changing cones.

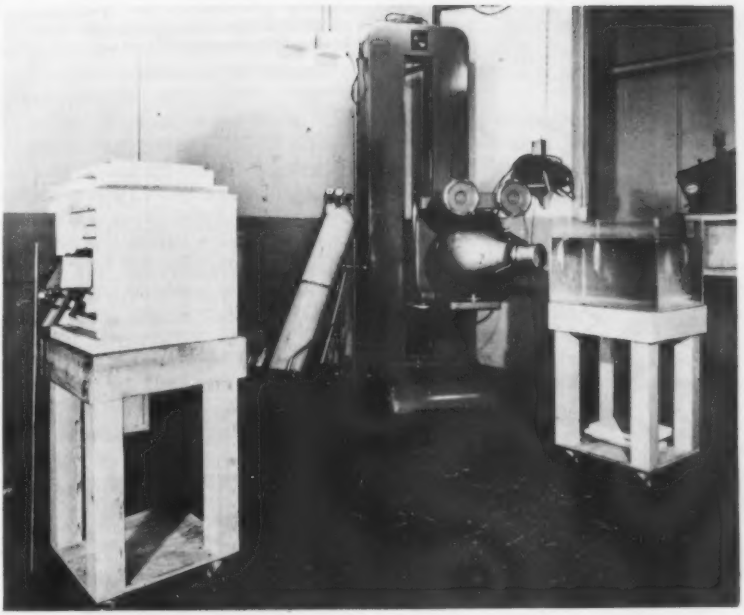


EXHIBIT 30.—Measurement of area of shielding of cobalt 60 teletherapy machine using nesting marble boxes, made by the Marble Institute of America.

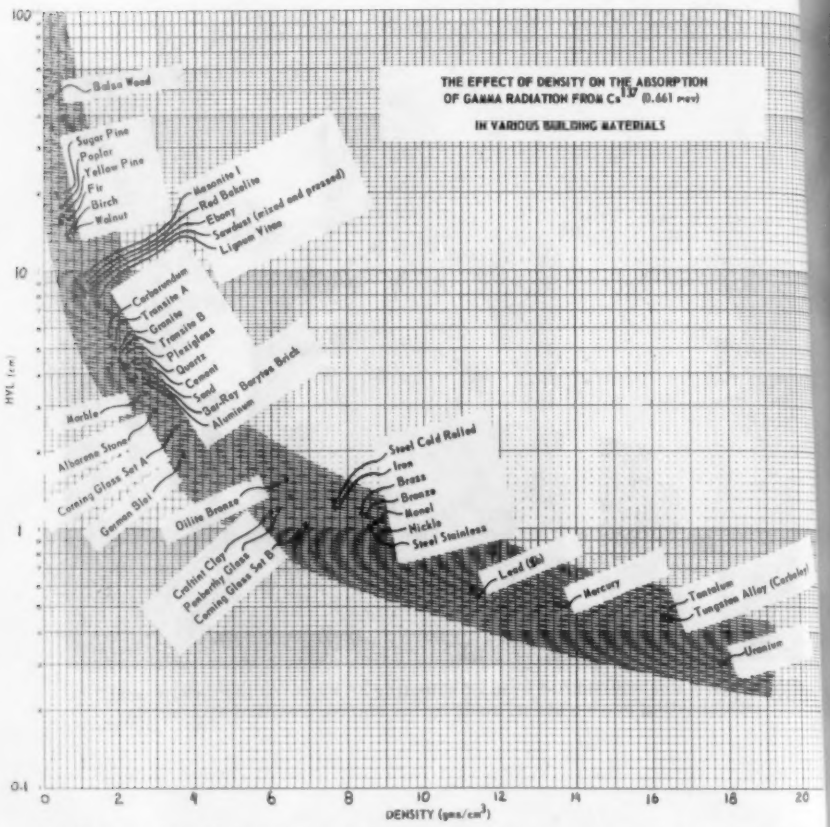


EXHIBIT 31.—Materials for shielding personnel from scattered radiations from teletherapy machines.

Representative HINSHAW. What thicknesses are indicated in that chart?

Dr. BRUCER. The thicknesses that are usually needed are up to about 2 or 3 feet of marble for the direct beam, and one-half foot for the scattered radiation.

Representative HINSHAW. That is a good-sized block.

Dr. BRUCER. There is more to the development of a teletherapy device than just the design of a machine. We also have to measure the amount and the kind of activity and the shape of the beam that comes out from the machine. Figure 19 (exhibit 32, p. 54) shows a part of the gadgetry that has been developed for measurements of this kind. From such a device we can get a complete picture of an external beam going through water, which simulates the human body, or we can measure the radiation around a phantom internal organ placed in a large volume of water to simulate natural conditions.

Let's go on to another item. To find out the economically best way to make a particular cobalt 60 source, we have conducted a study of the economics of cobalt source production. First, the cost depends upon the size of the cobalt source; a big source is cheaper than a small-sized source. Second, it depends upon the length of time that the cobalt is left in the nuclear reactor. If it is left in for a long time to make a high specific activity source, it is expensive. If it is left in for a short time to make a low specific activity source, it will be cheaper. The three-dimensional chart in figure 20 (exhibit 33, p. 54) shows the size of the source, the length of time the source is left in the nuclear reactor, and the dollars-per-unit radiation that comes out. And we see from this that the best area and most economical source design is in this area.

Representative HINSHAW. "In this area" could be described as what?

Dr. BRUCER. The area where the lower flux nuclear reactor can produce the cobalt.

Representative DURHAM. How about the half life? Is it just as long?

Dr. BRUCER. It is just as long as any other source. Nothing can change the characteristics of the cobalt 60.

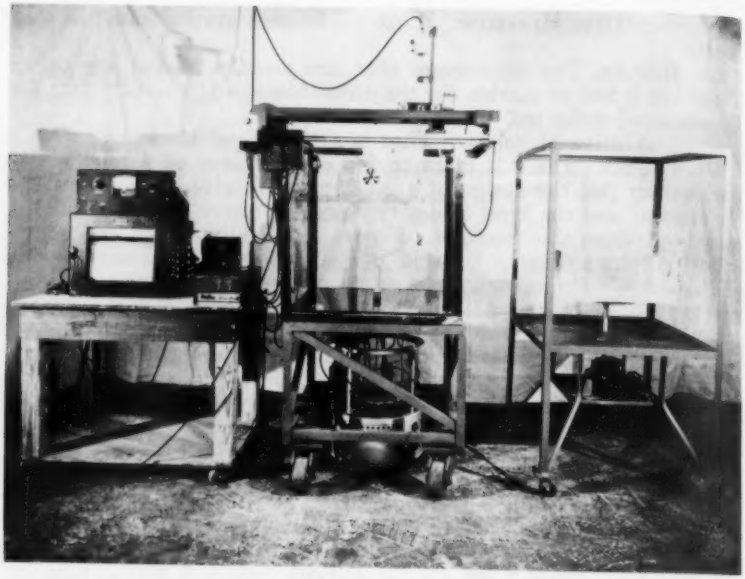


EXHIBIT 32.—An automatic isodose plotter to measure the radiations omitted by teletherapy beams and other isotopes.

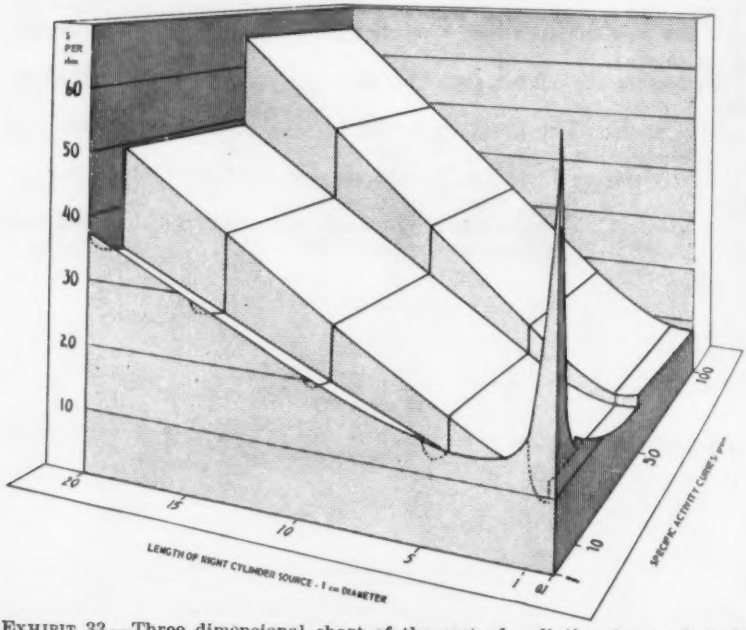


EXHIBIT 33.—Three dimensional chart of the cost of radiation from cobalt 60 sources of various sizes.

One of the big problems in making the cobalt machine a practical device is the incapsulation of the source itself. You can't just use a piece of raw cobalt since it will rust and flake. If each machine uses a different kind of loading mechanism then everybody will have to pay for a hand-made special job of tooling. However, if all cobalt can be put into a capsule that can be uniformly transferred from machine to machine, then everybody will get the economic advantages of mass production. Some machines are being made for 2,000 curies of cobalt 60, some for 1,000, some for 500 curies. If a source of 2,000 curies could be transferred at the end of 5 years to the next smaller machine without reloading or opening the capsule, this would spread the effective economic value of the cobalt over a much longer period than the 5-year half life of the cobalt.

Representative HINSHAW. That is what I was going to ask. Five years is the half life?

Dr. BRUCER. Yes. This means that if one has a 2,000 curie machine, then the source is not good when it decays much below a thousand curies.

Representative HINSHAW. Do you originally put in 2,500 curies and expect to use the source through a decay down to 1,500 or 1,400 curies or something of that sort?

Dr. BRUCER. This might be done, but then that source is wasted unless it can be placed in the next smaller machine. In order to do that, the incapsulation must be uniform, and all machines must use the same capsule. Therefore, we got together, not a group of scientists, but a group of about 14 producers of X-ray equipment, all of those in this country who are interested in the production of cobalt machines. We proposed the kind of standard source capsule shown in figure 21A (exhibit 34, p. 56). They did not agree with us. And at the end of three meetings, a standard source capsule, as shown in figure 21B (exhibit 35, p. 57) was finally adopted by the entire X-ray industry as a standard capsule for both Canadian and United States cobalt 60 sources.

Another factor which must be investigated very carefully is the amount of stray radiation that bathes all the other parts of the body when a tumor is being irradiated. Such radiation can be exceedingly dangerous. To study this problem, we have developed a "standard man," following the standard height, the standard weight, with certain other dimensions as determined by the International Commission on Radiation. We have built, as shown in figure 22 (exhibit 36, pp. 58 and 59) a standard-man phantom, which contains a liquid which reacts with radiation. We can measure in each compartment of the body the amount of radiation received by that compartment of the body under various types of radioisotope therapy. This will show us how good or bad are our designs of these various teletherapy machines.

In going through all kinds of problems with all kind of isotopes, and since we have so many to pick from, there are a number of things we have to consider. One of the important considerations is the question of energy absorption shown in figure 23 (exhibit 37, p. 60).

If we try to do therapy, where penetration is necessary and there is no advantage to a difference between the absorption of the energy in bone, muscle, and fat, then we would like to use an isotope with an energy up in the range of cobalt 60 or of cesium 137. Such an isotope is similar to the range of the 2-million-volt X-ray spectrum. If, however, we are trying for a diagnostic purpose to differentiate be-

tween such things as bone, muscle, and fat, then we must look for isotopes down in this lower energy range.

In figure 24 (exhibit 38, p. 61) we show a number of brachytherapy devices. These are exactly the opposite of the teletherapy devices. In brachytherapy we try to get as close as possible to the tumor. This was tried with radium many, many years ago. But radium is exceedingly expensive. Cobalt in this case is not very expensive. The problem is to make a metal that is completely corrosion resistant in body fluids. The International Nickel Co. has made a number of such metals for us to test. If we can find a sufficient corrosion-resistant alloy of cobalt, then by placing these various devices in the nuclear

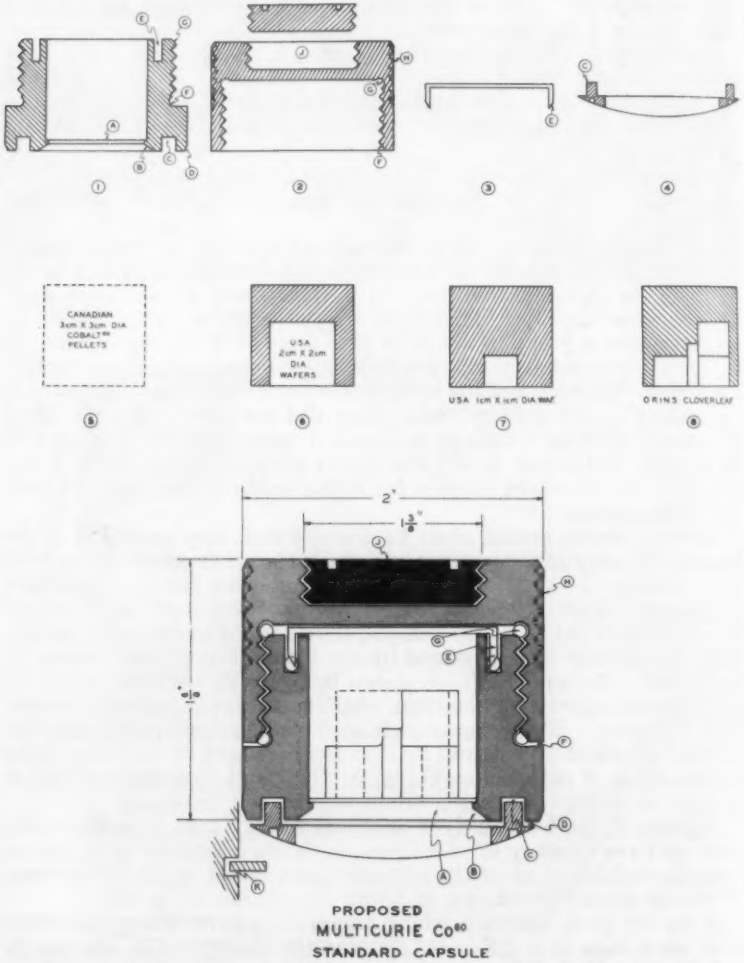


EXHIBIT 34.—First prepared design for a standard cobalt 60 source capsule.

reactor, we can make very cheaply any kind of therapy device even though each is very limited in its function. For example, one of these pieces is made to be placed behind the eyeball. The beads are made for the treatment of cancers of the sinuses. They are good at no other place, but they may be good in that particular place.

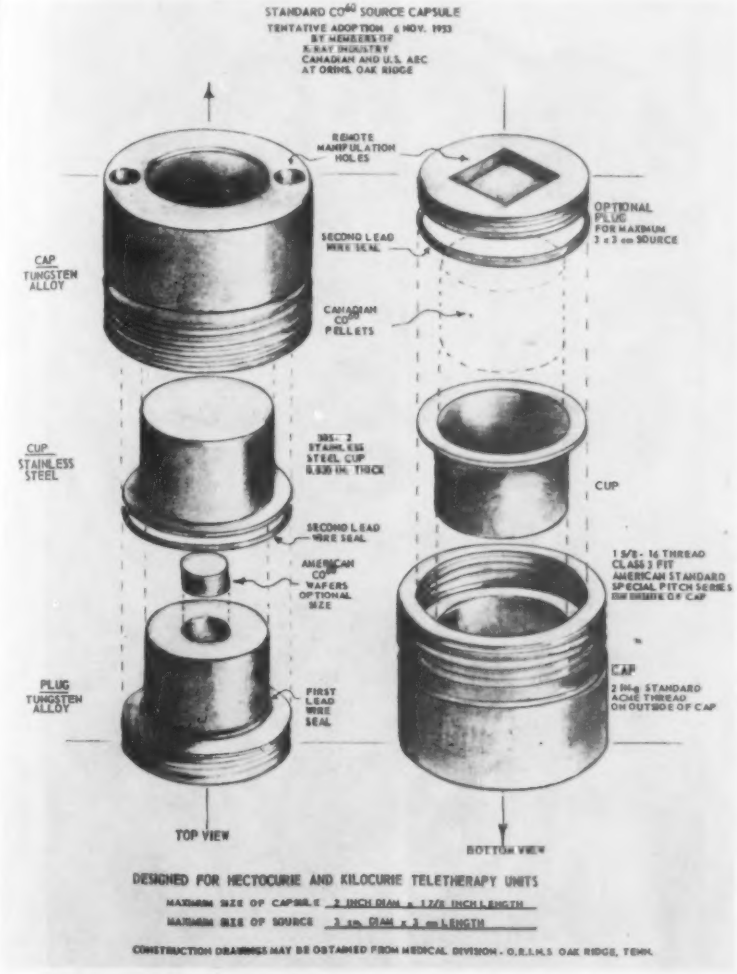

STANDARD Co60 SOURCE CAPSULE
TENTATIVE ADOPTION 6 NOV. 1953
BY MEMBERS OF
X-RAY INDUSTRY
CANADIAN AND U.S. AEC
AT ORINS, OAK RIDGE
REMOTE MANIPULATION HOLES
OPTIONAL PLUG FOR MAXIMUM 3 x 3 cm SOURCE
SECOND LEAD WIRE SEAL
CAP TUNGSTEN ALLOY
CANADIAN Co60 PELLETS
CUP STAINLESS STEEL
305-2 STAINLESS STEEL CUP 0.020 IN. THICK
CUP
SECOND LEAD WIRE SEAL
AMERICAN Co60 WAFERS OPTIONAL SIZE
1 5/8 - 16 THREAD CLASS 3 FIT AMERICAN STANDARD SPECIAL PITCH SERIES
CAP
2 1/16φ STANDARD ACME THREAD ON OUTSIDE OF CAP
PLUG TUNGSTEN ALLOY
FIRST LEAD WIRE SEAL
TOP VIEW
BOTTOM VIEW
DESIGNED FOR HECTOCURIE AND KILOCURIE TELETHERAPY UNITS
MAXIMUM SIZE OF CAPSULE 2 INCH DIAM x 1 7/8 INCH LENGTH
MAXIMUM SIZE OF SOURCE 3 cm DIAM x 3 cm LENGTH
CONSTRUCTION DRAWINGS MAY BE OBTAINED FROM MEDICAL DIVISION - O.R.I.N.S. OAK RIDGE, TENN.

EXHIBIT 35.—Final design for a standard cobalt 60 source capsule.

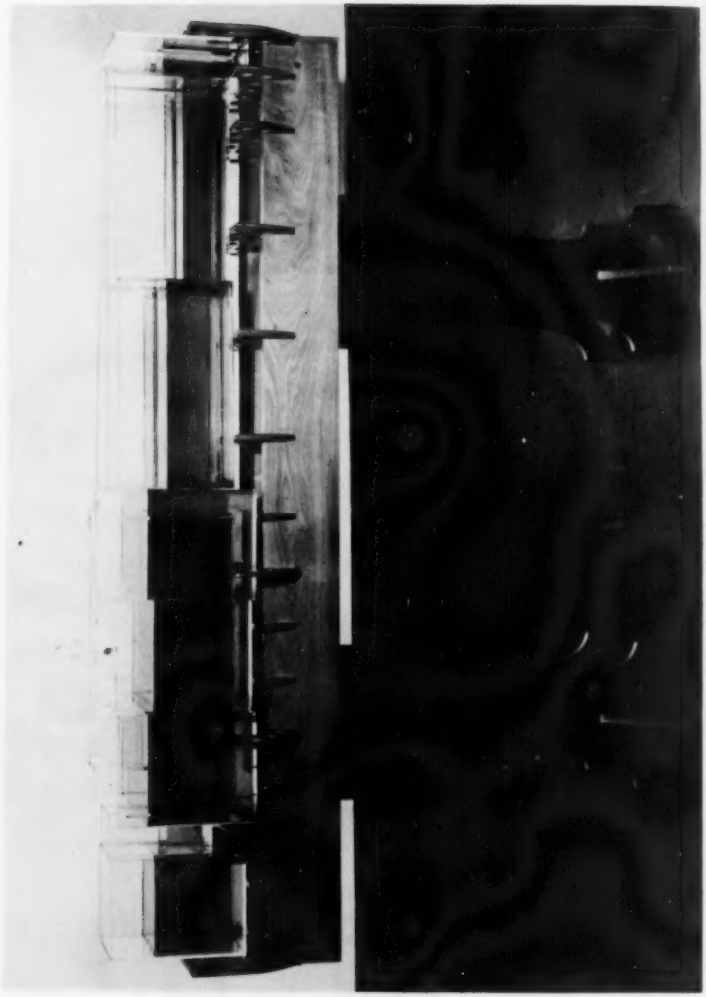
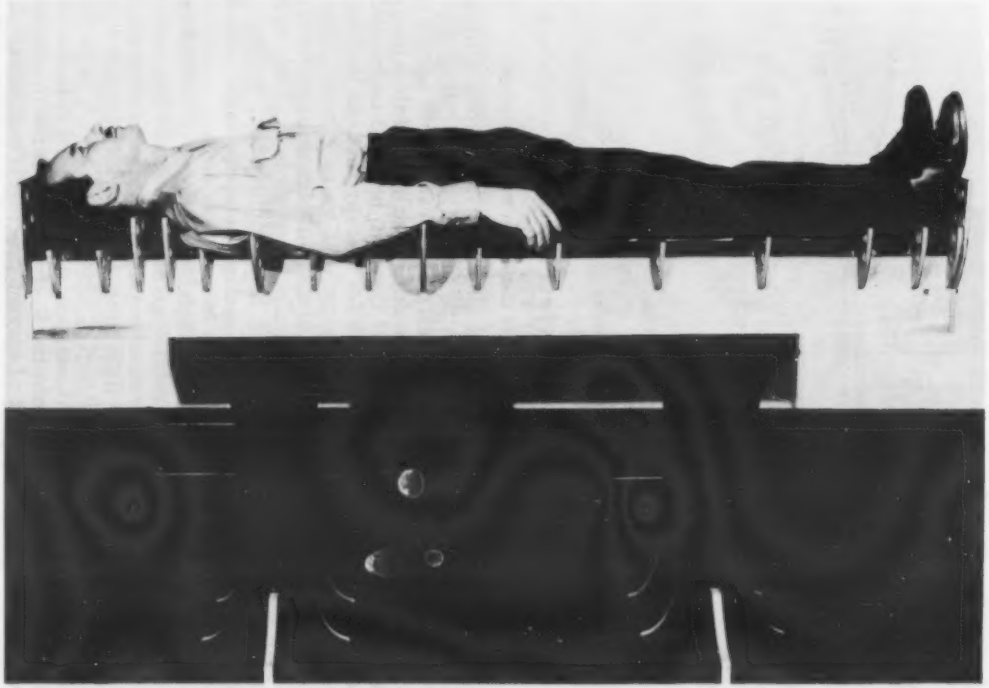


EXHIBIT 36.—The "standard man" phantom for the study of radiation dosage.

EXHIBIT 36.—The "standard man" phantom for the study of radiation dosage.



(NOTE.—Normal man for comparison with "phantom" above.)

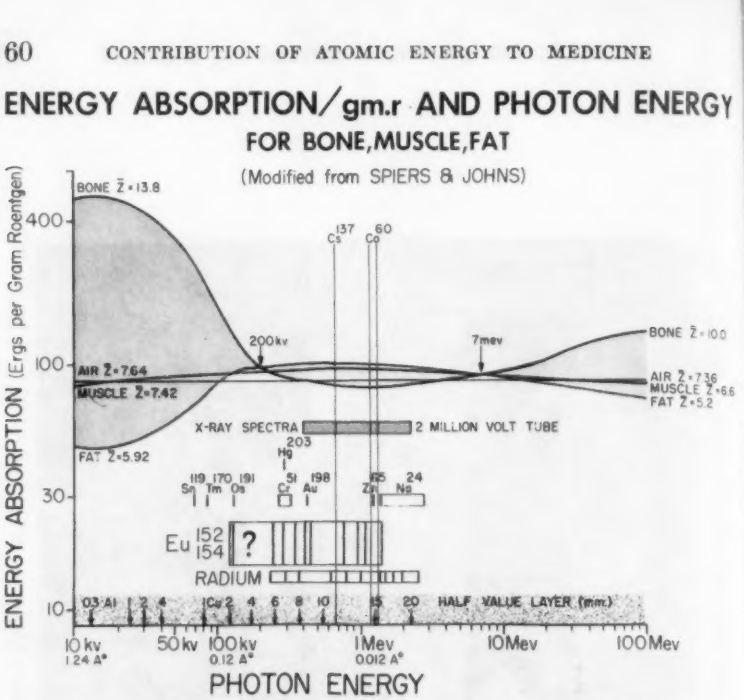


EXHIBIT 37.—Energy absorption in tissues for various isotopes.

Another size is used for packing the bladder in cancers of the urinary bladder. Another sized gadget can be made for the treatment of a carcinoma of the lip or a series of small plaques can be built up to many shapes and placed over cancers of the skin. Each one of these gadgets has a very limited usefulness; but if they can be made economically practical, they can be made available for therapy that can be done as efficiently as any other kind of therapy that we now have. This is not a new idea. It is a relatively old idea. But because of the development of the nuclear reactor, it is finally being made available to the medical public. I think the biggest responsibility that we have in our program is to make these radioactive isotopes available to the medical public.

The following outline with its explanatory notes is divided into sections which logically follow the type of work done. The sections do not represent an administrative or personnel organization nor do they represent a permanently fixed program analysis except in broad outline. Approximately one-third of the program cost is in the field of the internally administered isotopes; another third is in the field of external sources of radiation; the final third is on the routine program. Each quarter a report of current progress is published. Approximately 60 reports have been published in the open medical literature. About 30 special mimeographed reports have been made to the consultants to the division and the proceedings of 30 teletherapy meetings have been given worldwide distribution.

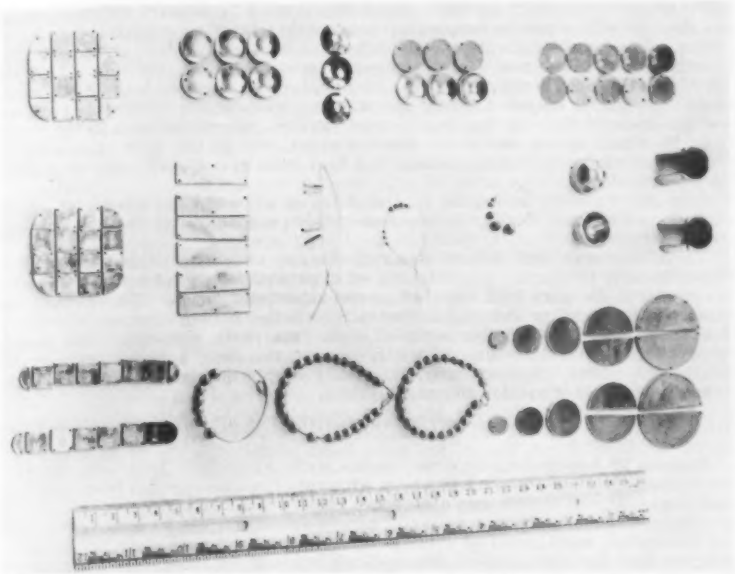


EXHIBIT 38.—Experimental brachytherapy devices from special corrosion-resistant metals made by the International Nickel Co.

PROGRAM OUTLINE OF THE OAK RIDGE INSTITUTE OF NUCLEAR STUDIES, MEDICAL DIVISION, UNDER CONTRACT WITH THE UNITED STATES ATOMIC ENERGY COMMISSION

I. INTERNALLY ADMINISTERED ISOTOPES

A. BASIC STUDIES

(Medical Division laboratories and animal farm laboratories. Kyker, in charge, Brucer, Hayes, Tyor, other members of the staff, and consultants)

A major objective in the basic studies is one of controlled localization or immobilization of radioactive substances in a particular organ, tissue, or compartment. The purpose is that of projecting practical approaches to therapeutic procedures. Colloidal systems and ionic solutions that behave like colloids in tissue comprise the substances that are under investigation.

1. Studies in intrapleural chromic phosphate in animals

"Colloidal" chromic phosphate containing phosphorus 32 stands among the first of the radioactive preparations to be investigated for internal therapeutic application. Difficulties attending its production in a reproducible manner contributed to a shift of interest to other colloids among which colloidal gold has received most attention. Certain investigators have recently resumed interest in chromic phosphate. The renewed interest includes both intracavitary use and interstitial use in prostate carcinoma.

In July 1952, attention was called to the possible usefulness of chromic phosphate. Very sparse data were to be found in the literature that pertained to interstitial and intracavitary studies. Investigators had given considerable attention to intravenous studies in small animals. A project was set up collaboratively with Dr. J. H. McAllister of Duke University (on resident-physician contract). The distribution of radioactivity following intrapleural administration of the "colloid" was studied in a series of rats and a few dogs. Subsequently

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(February–April 1953) a similar series was studied to compare different batches of the "colloid" since its commercial preparation involves empirical mechanical steps. The results indicate a wide difference between batches, primarily in the fraction of the dose that leaves the cavity promptly after injection. After the first day the results are practically identical. The fraction leaving the cavity rapidly is largely excreted so that the pattern is quite similar when it is expressed on the basis of the retained dose. More than 90 percent remains in the cavity. The liver and spleen ordinarily contain about half of the activity outside the cavity. Mediastinal tissues show a very high activity. Distribution on surfaces is in splotches.

The results were presented to the division of medicinal chemistry of the American Chemical Society in September 1953; a manuscript for publication is in preparation.

Three elements that behave like colloids are under investigation: yttrium, lutecium, and holmium. The selection of 25 potentially useful nuclides described by Brucer in January 1952, directed special attention to these. His selection was based on availability and radiochemical properties rather than on behavior in the body. The selected list included eight rare earth elements. The present study began with lutecium, which is one of the very rare elements of the lanthanide series. Subsequently, the study of yttrium overshadowed that of lutecium because of availability of materials.

2. Influence of amount of carrier on distribution of internally administered radioisotopes

Yttrium 90 has undergone considerable study since July 1953, and the work continues. Most of the work has been with rats though some has been with mice and dogs. It was shown that differences in pH from 2 to 7 had very little effect on the mobilization of intracavitarily administered yttrium 90 with carrier. In all subsequent work, a pH of approximately 4 has been used since hydrolysis of yttrium and the formation of radiocolloids becomes significant at a higher pH. The effect of the size of the chemical dose or the level of carrier was studied intraperitoneally and intrapleurally in rats. Both series permit quite similar conclusions. The preparations of radioyttrium varied in quantity of carrier from zero to 5 milligrams per milliliter. The fraction of the dose remaining in the site of injection showed a prominent relation to the level of carrier. Little effect appeared below a concentration of 10^{-6} M. At higher concentration, retention of the dose in the injected site rose sharply and leveled off at a concentration of about 10^{-3} M yttrium. Semilogarithmically, a plot of the data yielded a smooth sigmoid curve. The effect of pH and carrier was reported to the division of biological chemistry of the American Chemical Society in March 1954; a manuscript for publication is in preparation.

Using preparations of radioyttrium containing 1 milligram of stable yttrium per milliliter in physiological saline and adjusted to pH 4, the distribution has been studied in a large number of animals grouped according to the route of administration. The routes include intrapleural, intraperitoneal, intramuscular, subcutaneous, intravenous, intratumoral, and intraglandular administration. Radiochemical assay and autoradiographic records of a wide variety of tissues have been made. All of the results indicate consistently that yttrium with carrier behaves like a colloid and is effectively immobilized in the injected area. Intracavitary and interstitial application is suggested since immobilization is ordinarily as much as 98 percent of the adminstered dose for as long as two half-life intervals of the isotope. Studies of toxicity reported from other laboratories suggest no pertinent limitation on the effective level of carrier. The small fraction of the dose that distributes systemically is about one-half in liver and spleen. Excretion and skeletal uptake are both quite low but increase gradually with time. The activity of mediastinal nodes in the intraperitoneal series suggest that the slight spread of the material by way of lymphatics is prominent. Autoradiographic records of surfaces of injected cavities show a more regular uptake of activity than that which obtains with chromic phosphate. The distribution of radioyttrium by various routes of administration was reported to the American Society of Biological Chemists in April 1954, and a manuscript for publication is in preparation.

Intraperitoneal studies of the radioyttrim preparation in Ehrlich ascites tumor mice are in progress. This work was motivated by certain observations pertinent to colloidal gold, chromic phosphate, and the first clinical data to be obtained with tracer doses of yttrium. Whereas gold and chromic phosphate both leave the fluid and deposit on the surface of the cavity quite rapidly,

yttrium deposited on the serosal surfaces slowly and partially. In healthy experimental animals, yttrium was found to appear on surfaces at a rate and an extent comparable to those of chromic phosphate. Iodinated human serum albumin is shown to equilibrate rather rapidly between ascitic fluid and plasma of patients and does not concentrate on serosal surfaces as do other colloids. Yttrium, therefore, seems to stand between different types of colloids in its behavior. About half of it may deposit on the surface and about half may remain in the fluid but retention inside the cavity is almost complete. A series of mice studied at different stages of Ehrlich ascites tumor have given results that conform closely to the preliminary data in human beings. This provides a tool at the level of studies in animals to anticipate, with some confidence, the behavior of this and other similar materials at the clinical level.

In recent months procedures have been designed to simulate interstitial use of radioisotopes in the prostate and parametrium of the human being. The project was conducted collaborately with Dr. Julio Toriello, from Massachusetts General Hospital (on resident-physician contract). The series included 6 male and 6 female dogs divided equally between 3-day and 1-week periods to represent approximately 1 and 2 half-intervals of radioyttrium 90. At autopsy, 10 or 12 distal samples of various tissues were taken to represent systemic distribution of the dose and a dissection of all retroperitoneal tissue from upper abdominal to lower pelvic level was done. The specimen in one block was mapped autoradiographically and all discrete areas of activity were excised. These areas comprised 30 to 40 additional specimens. Each was radioassayed and the specimens of all well-defined areas were cut in half for histological identification as well as radioassay. The data are yet incomplete and very little interpretation has yet been attempted. Currently data suggest a high retention in the injected area and a spread into the pattern of surrounding lymph nodes. If these impressions continue as the data are analyzed the import on clinical application becomes obvious.

A further project with yttrium was planned a few months ago and is being pursued this summer with Dr. Robert A. Woodbury, University of Tennesse (a summer research participant). Since the effect of carrier is so prominent on localization, it is of interest to determine the effect of a previously induced body pool of yttrium on the distribution of carrier-free yttrium. The possible application relates to the effect of a dose or doses of stable yttrium before the use of tracer or therapeutic doses.

The study of lutecium, and more recently of holmium, has continued concurrently with the study of yttrium. The objective is one of comparison of different members of the lanthanide series of elements. The possibility that their almost identical chemical properties produces a similar biochemical behavior is of much practical interest. If this similarity does not prevail it becomes possible to generalize about others on the basis of this studied. If a similar behavior obtains there is then available a host of radioactive nuclides of these elements from which the desired radioisotopic property can be chosen for medical application.

3. Studies of lutecium

The distribution of lutecium (soft beta and gamma; $t\frac{1}{2}$, 6.8 days) as the chloride has been studied in more than 150 rats. There has been less freedom as compared with that of yttrium in arranging specific activity of preparations because of the rarity and expense of stable lutecium. The routes of administration have been more restricted—the intraperitoneal route, representing most of the intracavitary work, and the intramuscular route representing most of the interstitial work. Administration of similar quantities of radiolutecium 177 after different intervals of decay of the shipments afford a limited study of the effect of carrier. One shipment of lutecium produced in LITR yielded Lu 177 approximately two orders of magnitude greater in specific activity than did shipments from the graphite reactor. By this means it is observed that the effect of carrier defined for yttrium is also applicable to lutecium.

Lutecium complexed or chelated with Versene has been studied in a shorter series of animals. In contrast to the high localization of the chloride, the versenate is excreted quite rapidly by the kidney. As much as 95 percent of the dose ordinarily appears within 24 to 48 hours following administration. Further studies are contemplated to evaluate the efficacy of removal of the rare lanthanide elements from the body.

4. Studies of holmium

Whereas lutecium stands as the heaviest element in the lanthanide series, holmium is approximately one-third from the top of the series. Holmium also stands high along with lutecium in the list of potentially useful elements selected by Brucer. Stable holmium is 100 percent abundant as Ho 165 and therefore yields pure Ho 166 by reacting with a neutron. Holmium 166 emits an energetic beta particle, 1 hard, and 1 soft gamma ray; it has a short half life for clinical use but sufficiently long, 27 hours, for practical application. The experiemental work presently completed consists of studies in approximately 60 mice (intraperitoneal) and a short series of rats (intravenous). The observations are similar to those of yttrium and lutecium as far as the data permit comparisons.

5. Heterogeneous carrier effects

Most of the rare earth elements are quite scarce and expensive in a highly purified state. Conversely, crude fractions of groups of rare earth elements are used in certain industrial and commercial commodities and are relatively inexpensive. The first lutecium purchased for our experimental project came at $2 per milligram; more recently, by special arrangement it came for 50 cents per milligram. Perhaps 10 to 15 milligrams of the stable element would yield a therapeutic dose. Unlike most ordinary chemicals, these substances approach a cost that would be significant in the ultimate cost of a neutron-bombarded, processed, radioactive therapeutic agent. Studies have been in progress on what we have termed "heterogeneous" carrier both for the portended theoretical interest and also for the practical aspect of cost of a potential radiodrug. It was postulated that the chemical properties of different rare earths might be too close to be distinguished by the animal body, in which case one could serve as a carrier for another. Observations using separately yttrium and lanthanum as carrier for lutecium 177 confirm the hypothesis; that is, Lu 177 can be localized at the site of administration by either of these elements added as carrier. In a few experiments the indication is the same for controlling the localization of Ho 166. So far as is known the toxicity of rare earth elements in general is not high and the possibility exists in the use of crude rare earth mixtures for providing carrier at the level desired.

6. Comparison of Cs and Rb with potassium

The postulate that rubidium is a biochemical substitute for potassium has appeared in the literature for approximately 30 years and has been reinvestigated on several occasions. Renewed interest in the subject has derived from the availability of radioisotopic tools. It would be of great usefulness to use rubidium to measure the potassium space of the body since the former affords a nuclide of approximately 20 days half life, whereas the available isotope of K has a half life of only 12 hours. After Dr. Malcolm Tyor had accumulated some very interesting data on four patients that presented wide limits with respect to history and well-being, it was learned to our surprise that the stable rubidium that had been used for producing Rb 86 was contaminated with an unknown amount of stable cesium. The cross section of cesium for thermal neutrons is many times as large as that of rubidium. Thus a small percentage of stable contaminant yielded a large radiochemical contamination. It became of interest, therefore, to study in paralle! series of animals the behavior of rubidium and of cesium. The experimental work continues, as originally planned, and approaches completion in the near future. Six groups of 6 rats each are included: Groups received a mixed dose of potassium and rubidium; and 3, similarly, received potassium and cesium. Both the potassium series and the rubidium series were studied at 5 minutes, 1 hour, and 18 hours after administration. Specimens were taken from a wide variety of tissues. Each specimen was assayed for both radioactive constituents. A comparison of the ratio of Rb and Cs to potassium to the ratio of the same elements in the administered dose was taken as an index of the extent to which these alkali metals duplicate K in their metabolic behavior. Interpretation of the data awaits completion of the experimental series.

7. Studies on sulfur

Sulfur 35 has been applied as a tool to the study of two problems. Both are incomplete and have suffered interruptions repeatedly because of the demand by concurrent projects on the personnel available for this work. One of these relates to the mechanism of the incorporation of sulfate into chondroitin sulfate.

The reaction was studied in vitro using stable chondroitin sulfuric acid and radioactively tagged inorganic sulfate. In a later phase, radioactive chondroitin sulfate was biosynthesized and isolated from the cartilage of a dog that had received sulfur 35 as sulfate. No exchange was observed in vitro. Several publications by Bostrom, Gardell, and others from Instituto Karolinska, Stockholm, appearing late in 1953, became available to us in February 1954. Their excellent work supersedes that done in our laboratory. Interest continues in inorganic sulfur metabolism in relation to the claim that there is a prominent uptake of the sulfate ion in chondrosarcoma. The project requires a redrafting of objectives on the basis of the recently published work.

The other problem employing sulfur 35 is accessory to one of the clinical studies. Sulfur labeled methionine was administered to a patient with myelogenous leukemia. The urinary sulfur 35 was assayed in approximately thirty 24-hour specimens by different methods of assay. Similar studies of frozen plasma samples are contemplated. The work is to be resumed as soon as opportunity permits.

8. An appraisal of liquid counting techniques of various isotopes

Considerable attention has been given to methodology pertinent to the use of radioactive tools. Certain procedures are summarized briefly in that which follows:

The radioassay of a specimen of tissue or excreta for its content of a beta emitting isotope is most easily done by counting liquid samples. It is necessary to prepare a homogeneous digest; this is approximated by brief treatment with boiling nitric acid. Of the various cations that have been or are being studied in our laboratories, the nitrates of all are quite soluble. We have studied in considerable detail the instability in counting rate that may be observed in a diluted aliquot of a liquid sample by end-window GM tube counting. Certain elements such as gold and hafnium show a pronounced increase in counting rate upon standing. The apparent increase is undoubtedly due to a surface phenomenon resulting in a higher concentration on the surface membrane. The effect of numerous factors including the composition of the sample dish, the nature and concentration of acid, surface active agents, complexing agents, carrier, and others were observed. The mechanism is not easily interpreted but the occasion of error that may be greater than 200 percent, cannot be overlooked. The liquid counting of beta emitters requires preliminary evaluation of the stability of the counting rate to yield valid observations.

9. Tissue digestion methods

Various methods for rapid "wet-way" digestion of specimens of tissue have been compared. The frequently used concentrated nitric acid does not satisfactorily degrade fats. Perchloric acid, used by some routinely, affords a distinct explosive hazard. Concentrated sulfuric acid offers a possible approach under conditions simulating those of the Kjeldahl method. A procedure was devised combining preliminary digestion with nitric acid in the presence of copper followed by digestion with sulfuric acid and hydrogen peroxide. The procedure works well with some isotopes; with the use of certain special apparatus and equipment it is satisfactorily rapid.

10. Preliminary studies on a rotational counting device

The end-window counting of very soft beta emitters, such as C 14, S 35, and Ca 45, is important to many biochemical and medical studies. The satisfactory preparation of a plaque of an isolated compound containing the radioisotope is technically difficult. Errors attributable to self-absorption are very important; unevenness or cracking afford additional variations. A device that spins the plaque slowly and rotates it eccentrically with respect to the window of a GM tube should provide statistically similar geometry for all points on the plaque. Considerable data have accrued from manually duplicating the device. The data suggest further work. A suitable device is designed but not yet built.

11. Measurements of pH in radiochemical preparations

The pH of radioactive preparations intended for internal administration is of obvious importance. It is undesirable to use a glass electrode instrument routinely because of cross contamination by the dipping electrode. Colorimetic comparison with a series of buffer standards or indicator papers is relatively inaccurate. A spectrophotometric method in which the concentration of indicator affords no appreciable error has been designed and evaluated. The method depends upon a functional relationship of pH to the ratio of optical density

readings of the two colors of the indicator. The data have been interpreted and publication awaits preparation of the manuscript.

12. Procedure for interpreting gross autoradiograms

A procedure has been designed and is used routinely for the interpretation of gross autoradiograms of a slice of tissue through more than one organ, such as a transverse section of the pleural viscera.

13. Separation and chemistry of gallium 67

Prior to the study of carrier-free Ga 67 (a cyclotron produced isotope) as a possible therapeutic agent in the treatment of bone malignancies, it was necessary to develop a method for its separation and purification. During the course of this work a study was made of the distribution of Ga 67 between hydrochloric acid solutions and various ethers. The method finally adopted employs diisopropyl ether. A report on this method, together with a description of the remote control apparatus used, is being prepared at present.

14. Distribution of porphyrin and metalloporphyrin in normal and neoplastic tissue

An investigation of the distribution of hematoporphyrin between normal and neoplastic tissues in mice was initiated on the basis of findings reported in the literature. In limited experiments no concentration of this porphyrin in neoplastic tissue over that found in normal tissue was observed. The study has been discontinued at present.

15. Metabolic distribution in corrosion resistant metals

In the design of brachytherapy devices one of the limiting factors has been the necessity for complete corrosion shields over the source of activity. If an alloy of the source isotope could be used without the necessity for a corrosion shield, brachytherapy devices could be made cheaply and are unlimited in shape and usefulness. The International Nickel Co. has made a number of corrosion resistant alloys containing cobalt. The irradiation and radiation characteristics of these are being studied. Beads, plaques, and needles made of the metals have been placed into the tissues of living rats. Upon sacrifice after 3 weeks of exposure, it is found that only insignificant amounts of cobalt 60 leave some alloys and appear in the liver and other organs of the animal. In high cobalt alloys there is a greater likelihood of cobalt entering the metabolic pathways. The problem is being studied in a series of alloys and raw metals.

16. Mechanisms for preparing powdered sources

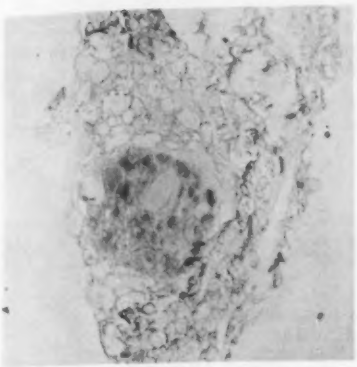
Some isotopes cannot be made except in powdered form. The addition of small amounts of ductile metals allows some shaping of the source and makes these sources easier to handle. There is in progress a study of the best way to load and prepare some of the more unusual powdered source materials.

B. CLINICAL STUDIES

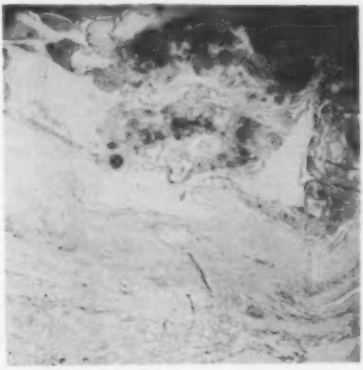
(Andrews, in charge, Cooper, Kniseley, Palmer, Root, Tyor, Brucer, Sutliff, and other members of the staff, and consultants; exhibit 39, p. 67.)

1. Therapeutic uses of colloids

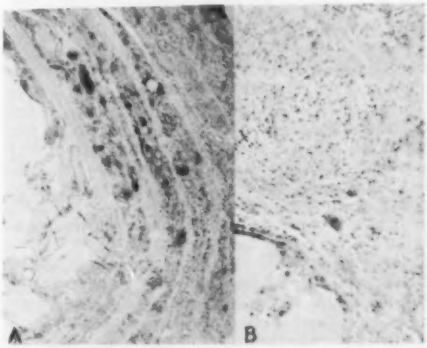
(*a*) *Intracavitary use.*—The intracavitary use of colloidal radioisotopes has been a major project for over 3 years. This form of treatment, which was originated in Europe, has been studied here from a rather fundamental point of view, with emphasis upon the gathering of specific information on the metabolism, distribution, and histopathologic effects. At the present time we are using colloidal Au 198 in the treatment of effusions in patients with a relatively favorable outlook, in whom we hesitate to use an untried agent, such as Y 90, now under study. Most of the patients in this group admitted at the present time are given a tracer of Y 90 for the purpose of obtaining information, and later are given a therapeutic dose of Au 198. We are continuing to make follow-up observations on the pathologic effects of Au 198 as opportunities arise. (Four publications on intracavitary gold 198 have been presented.)



Example of microscopic autoradiogram demonstrating hyperfunctioning nodule in thyroid gland. Earlier therapy for hyperthyroidism (7.5 mc of I 131) had not produced a destructive lesion histologically demonstrated at this time.



Microscopic autoradiogram of hyperfunctioning nodule in autoradiogram in comparison to the compressed rim of normal thyroid. Radioassay confirmed the variation in uptake.



I–131 microautoradiogram of nodular thyroid. Uptake is small follicles in the capsular region and in the adenoma. B. shows marked alteration of nonnodular thyroid tissue. This is an effect of older therapeutic I–131 dosage for hyperthyroidism.

Au 198 microautoradiogram of transurethral biopsy of prostate. Interstitial Au 198 had been injected transversically 10 days prior to biopsy. There is uneven distribution of the isotope and no histological effect on the neoplasm in this area.

EXHIBIT 39.—Microscopic autoradiograms of tissues.

Chromic phosphate containing P 32 has been tried as a substitute for Au 198. The lack of any significant gamma emission reduces the hazard to personnel and may give a more suitable localization of the radiation dose to the patient; its half life is longer and hence it is easier to ship to distant localities. The chromic phosphate has been produced (by Abbott Laboratories) apparently with some difficulty and lack of uniformity. It dissociates somewhat and when the material is given into body cavities a significant amount is excreted in the urine. Another evidence of this dissociation is the presence of a significant amount of inorganic phosphorus in red cells. With this isotope our efforts were chiefly to obtain information on its behavior. Our series was too small to allow evaluation of clinical effects. (A publication on this is in press in Radiology.)

Yttrium 90 is under investigation as another isotope for intracavitary use. Interest in its clinical potentialities arose from the animal work of Dr. Kyker and others of our staff. In a small number of patients studied it has been shown to remain well localized in the region of the cavity, with negligible blood levels and excretion. The basic types of information obtained for colloidal Au 198 and chromic phosphate (P 32) are being obtained for Y 90.

(*b*) *Intravenous use of colloidal Au 198 in the treatment of chronic leukemia and certain cases of lymphoma.*—The intravenous use of colloids has also been studied. Colloidal Au 198 has been tried as a form of therapy for certain tumors of the liver, and has been found worthless in most cases. (Publication in press, Cancer.)

Similarly, following the work of Hahn, colloidal Au 198 is being given for the treatment of certain cases of chronic granulocytic leukemia. (An abstract of this work has been published, Central Society for Clinical Research, 1953, and a more complete report is in preparation.)

(*c*) *Interstitial use of colloids.*—The interstitial injection of colloids has not been undertaken as a major program, not because it was considered lacking in promise, but rather because it is believed that this is a field in which special surgical skills and technical equipment not now available are needed and because evaluation of results on a small number of cases is difficult. However, a limited amount of work has been done as part of the training program and for certain radio-assay and hematologic studies. We have studied two patients given injections of colloidal Au 198 into bronchial mucosa. These preliminary studies failed to show localization in mediastinal lymph nodes, which had been anticipated on the basis of work done in the dog by one of our former visiting collaborators. We also have had two patients with prostatic carcinoma treated by interstitial injection according to methods that have become almost standard elsewhere. This was done essentially as a part of the resident training program.

2. Study of metabilism and therapy of neoplasms involving bone

(*a*) Gallium 67 (exhibit 40, p. 69).—Following completion of the work on gallium 72, we have continued to study gallium 67 in bone lesions. The isotope is prepared by cyclotron bombardment and is relatively expensive. The rather complicated chemical preparation is carried out at the Medical Division under the direction of Dr. Hayes. It has been difficult to find patients in whom any satisfactory evaluation of effect could be made. Bone lesions are often very chronic and X-rays may fail to show their progression or regression. Laboratory tests, such as phosphatase determinations, have not been of much help; more complicated methods, such as total calcium balance studies, have not been undertaken because we did not feel that we could afford the facilities and personnel.

It has been found that at least a small amount of carrier is needed, with the Ga 67, to allow the best possible localization. Retention and local concentration is best in osteoblastic lesions. Stable chemical toxicity appears to be no longer a problem. Bone marrow damage is the chief factor limiting dosage. It is believed that some palliation, or at least prolongation of life, has been achieved, but this is only a clinical opinion, and the benefit appears to be quite slight. The data collected on tissue distribution, blood levels, and excretion, are extensive.

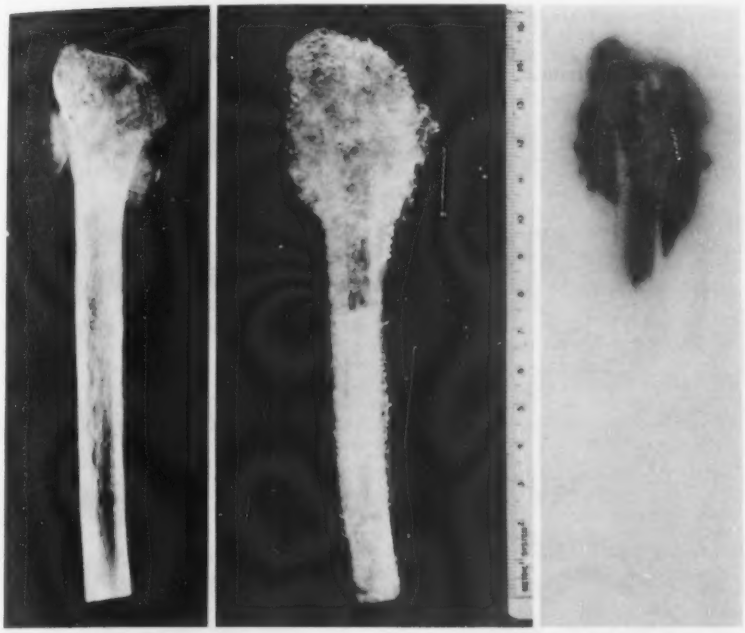


EXHIBIT 40.—Patient E. D. 410427. A tracer dose of 1.47 millicuries of Gallium 67 was given 18 hours before amputation. The osteogenic sarcoma shows an avidity for the gallium. The peripheral portion of the tumor invading soft tissues has the highest concentration. Normal bone shows relatively little uptake. Radioassays showed ranges of 0.44 to 1.0 microcuries/gm in samples of tumor; Yellow marrow .025 microcuries/gm; Cortical bone .025 microcuries/gm; Skin .0158 microcuries/gm.

(*b*) *Ca 45 in relation to primary and metastatic tumors of bone* (*exhibit 41, p. 70*).—A study of Ca 45 has recently been inaugurated as an independent study and as a means of understanding better the localization of gallium. We have performed autopsies on two patients who had been given tracer doses of Ca 45. Gross autoradiograms are being prepared and radioassays of selected tissues are in preparation. The doses of Ca 45 used (about 600 microcuries) are probably not large enough to allow preparation of microscopic autoradiograms; but an additional patient in terminal condition has been given a large dose (5 millicuries) of Ca 45. Arrangements have been made with the staff of the UT–AEC agricultural research project to allow the use of their special equipment for cutting undecalcified bone for gross autoradiograms.

(*c*) *Use of antimony 122 in myeloma.*—An investigation of radioantimony has been done but has not yet been prepared for publication. No further work on this is contemplated in the immediate future. There was no favorable localization of the antimony, which was given as fuadin, in the lesions of malignant plasmocytoma. Most of the isotope went to the liver where it remained for a long period.

3. Diagnostic and investigational uses of isotopes

(*a*) *External surveys of liver after administration of Au 198.*—Autopsy material obtained here over 2 years ago illustrated the striking way in which neoplasms of the liver are in contrast to normal liver tissue in that the tumors fail to take up colloidal materials. Efforts have been made to use this distinctive distribution as a diagnostic test, by giving colloidal Au 198 intravenously and following this with scintiscan studies of the abdominal wall. A lack of a suitable number of patients has limited this investigation. In general we have been

able to demonstrate large metastases or gross displacement of the liver, but we have not been able to show small unsuspected metastases. Autopsy specimens have been used for scintiscan records, autoradiograms, and tissue assays, as methods of determining the limitations of the method. (An abstract has been published.)

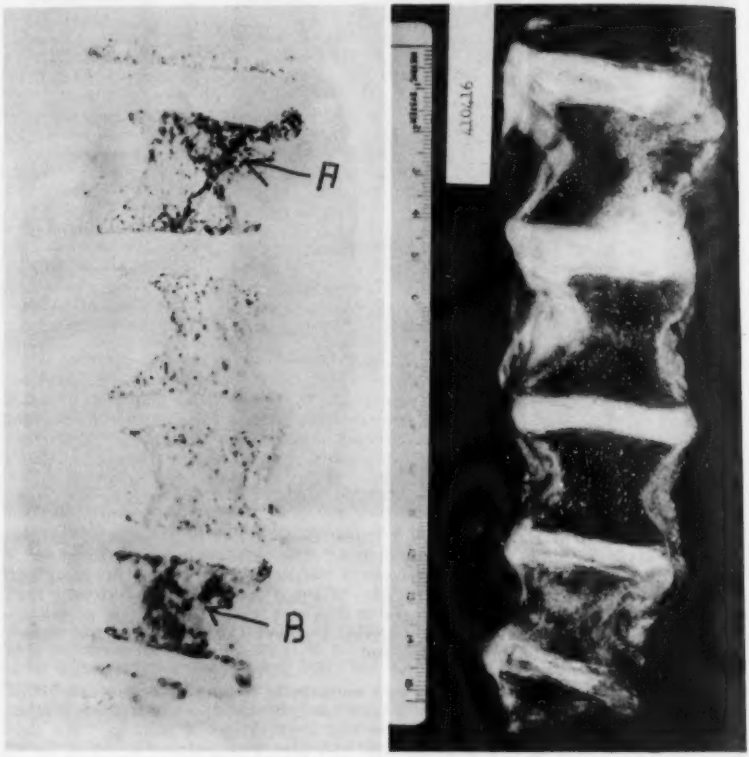


EXHIBIT 41.—Patient J. M. 410416. A tracer dose of 510 microcuries of Calcium 45 was given intravenously 21 days before death. A thin section of the vertebral column shows destructive metastases at site A. and B. The darker areas on the autoradiogram corresponds to the areas of metastases.

(*b*) *Rate of disappearance of tracer doses of Au 198 from blood as an index of reticuloendothelial function.*—In a few patients frequent blood samples have been obtained after the intravenous injection of colloidal Au 198. The disappearance from venous blood gives a complex curve with several components. The early phase usually has a half-time of between 3 and 4 minutes. With the number of patients studied up to the present we have not been able to correlate the curves with factors influencing hepatic blood flow or reticuloendothelial function.

(*c*) *Uptake of colloids by normal and pathologic leukocytes.*—The uptake of colloids in white cells has been the subject of some scattered measurements, made without ideal methods of separating the cells. More recently, better methods of separating the cells have been started. A more carefully controlled study is to be undertaken this summer by Dr. Eades and Dr. Ganz of the University of Tennessee Medical School.

(*d*) *Metabolism of sulfur labeled amino acids and inorganic sulfur.*—Investigations of organic sulfur metabolism using sulfur 35 have been done chiefly as an outgrowth of the interest of Dr. John Wood and his staff at the University

of Tennessee Medical School. We have been interested in the metabolism of S 35 labeled methionine in malignant plasmocytoma and rather extensive studies on one patient are underway. (One report on white cell organic sulfur uptake has been submitted for publication.)

(e) *Radioisotopes in relation to plasma protein fractions, as studied by paper electrophoresis.*—A similar part of the program, which is just being set up, is the more or less routine use of paper electrophoresis to study the state of various isotopes in relation to plasma protein fractions.

(f) *Red cell mass, plasma volume, red cell survival, and iron metabolism in malignant diseases, hematologic disorders and polycythemia.*—Methods have been established for red cell survival (Cr 51, Fe 59) and red cell and plasma volumes (Cr 51, P 32, I 131, albumin, Evans blue). The training program has required that these techniques be available. Many of these studies are incidental to the clinical program. Over a period of time, as clinical cases gradually become available, we expect to obtain data on some specific problems of interest to certain staff members—for example, iron metabolism in myelofibrosis.

(g) *Mechanisms of fluid collection in ascites.*—As an outgrowth of the intracavitary treatment of affusions, some work has been done on protein exchange in relation to fluid accumulations. (One paper is in press.)

(h) *Studies with K 42, Rb 86, and Cs 137.*—Studies on the comparative metabolism of potassium, rubidium, and cesium are being done on human patients. The first part of the work utilized differential counting techniques for simultaneous assay of samples containing both K 42 and Rb 86. (An abtract has been published.)

4. Investigations using I 131

(a) *Treatment of carcinoma of the thyroid and criteria for selection of cases for therapy. Histologic effects of internal radiation on normal, hyperplastic, and neoplastic thyroid tissue.*—A long, continued study on carcinoma of the thyroid has been in progress since the first patient was accepted in the Medical Division Hospital. As a part of this, a special interest has developed in the use of radioiodine to destroy the normal typroid gland. Histologic and autoradiographic observations have been made. A further outgrowth of this was a study of I 131 in dogs, and a newly begun project on the effect of radiation from external sources upon the histology of the thyroid and upon the metabolism of tracer doses of I 131. (A publication on the human work has appeared in the American Journal of Medicine. One on the first part of the work in dogs is in press in the American Journal of Roentgenology.)

(b) *Blood levels of radioactivity and paper chromatographic analyses of metabolized iodine compounds.*—Determination of blood levels of radioactivity and amounts of protein-bound (triochloracetic acid precepitable) I 131 have been made in large groups of patients. It appears that the amount of protein-bound activity in the blood is one additional factor helpful in indicating the degree of function of a thyroid tumor after the normal thyroid has been removed.

(c) *I 131 in the therapy of hyperthyroidism.*—Recently a few selected patients with hyperthyroidism have been accepted for I 131 therapy. This has offered us some clinical background for the training program and, in certain patients, an opportunity to observe further the histologic effects of this isotope on a different type of thyroid tissue.

5. Studies of bone marrow morphology with special reference to vascular pattern; effects of radiation on marrow; pattern of malignant invasion of marrow

Dr. Okwa, on a Damon Runyon Fellowship, has been studying bone marrow morphology, using newer techniques of arteriography and isotope techniques. The marrow has proved to be a difficult tissue to study by these methods, largely because of its fragile structure and because of the difficulties involved in cutting the surrounding bone cortex. Progress has been made with these technical problems.

6. The use of P 32 in blood disorders

We continue to treat and follow a group of patients with polycythemia vera, using P 32 in cautious doses, often combined with phlebotomy. No important research is under way in these patients, but some incidental studies are being obtained (Fe 59 disappearance studies, blood volume determinations). We have a special interest in the eventual state of the bone marrow in these patients.

We have treated, with P 32, a few patients having chronic leukemia. We have usually been unable to admit enough adult patients with leukemia to allow the desired studies with more experimental forms of treatment, and so P 32 has not been used very much.

II. The External Use of Isotopes (Brucer, in Charge, Harmon, and Other Members of the Staff, and Consultants)

A. THE TELETHERAPY EVALUATION BOARD

The Teletherapy Evaluation Board is an organization of 22 medical schools studying the specific problems involved in the use of radioisotopes as sources of energy for gamma ray therapy. About 25 percent of the cost of this program is borne by the schools, and the rest by the AEC. Two major projects are currently under study. One is the use of Cs 137 in a freely moving beam therapy machine. The other is a study of the necessary characteristics for a series of low and medium curiage teletherapy devices. The first practical medium curiage teletherapy machine designed from the deliberations of the TEB is now commercially available. The TEB is currently setting up a long range clinical program for the study of cobalt 60 devices.

B. THE INDUSTRIAL CONFERENCES ON TELETHERAPY, JOINTLY WITH THE ISOTOPES DIVISION OF THE UNITED STATES ATOMIC ENERGY COMMISSION

In cooperation with both the United States and Canadian producers of radioisotopes, the Medical Division has held a series of informal information meetings of all of the major manufacturers of radiation therapy equipment. The first practical result of these meetings has been the joint design of a tentative standard cobalt 60 teletherapy source capsule. Such a capsule will effectively reduce the economic cost of cobalt 60 sources and has been adapted to the designs of all of the commercially produced teletherapy machines.

C. ABSORPTION OF GAMMA RAYS FROM CO, EU, CS, AU, I, CE, HF, AND OTHERS

Particularly in reference to the isotopes commonly used in medicine, a series of attenuation measurements is being made in four kinds of materials. The study is basic to both dosimetry and protection problems. It has been almost completed for gold 198 and cesium 137 and is nearing completion for cobalt 60. The four kinds of attenuation materials are:

1. Elements and simple salts of elements.
2. Tissuelike materials of known composition.
3. Human tissue.
4. Building and shielding materials.

D. SHIELDING REQUIREMENTS FOR LARGE SOURCES

One of the major costs of teletherapy equipment is the cost of shielding the surrounding area. As a part of the teletherapy program both basic and practical measurements have been made in the following fields:

1. Wall type shielding for teletherapy rooms and large areas.
2. Narrow beam shielding under conditions approaching the Klein-Nishina assumptions.
3. Spherical broad beam close-in shielding with air scatter.
4. True broad beam conditions with scatter inside the shielding material.

E. THE DESIGN OF HIGH AND LOW CURIAGE TELETHERAPY UNITS

Each of the following units of a teletherapy machine is under investigation by the Division, other members of the TEB, and by certain members of the X-ray industry: The shielding head, the wedge filter, the on-off shutter mechanism, the continuously variable diaphragm, the suspension mechanism, the control panel, the light localizer, cone design, and the cam design and rotational control mechanism.

F. CHARACTERISTICS OF HUMAN TISSUE AS RELATED TO ENERGY ABSORPTION

As a part of the basic dosimetry study the following subjects are being studied as materials are made available:

1. Specific gravity and density.
2. Effective atomic number.
3. Attenuation coefficients at various energies.
4. Size, shape, and volume dosage.
5. Energy absorption at various energies.

G. COST PROBLEMS AND SOURCE DESIGN

This material has recently been released to the X-ray industry and is the subject of continuing study.

III. DOSIMETRY AND RELATED PROBLEMS (BRUCER, HAYES, AND OTHER MEMBERS OF THE STAFF)

A. The problem of dosage from internal sources—phantom studies on sources varying in:

Size Shape Isotopes (energy) Number of sources	in	Regular geometric phantoms Human volume phantom Simulated plastic human phantom Simulated human organs Excised animal organs

These studies will emphasize sectional volume and total volume integral dose measurements. A water-filled standard-man phantom has been designed and constructed for this purpose. It is felt that aqueous chemical dosimeter systems, systems in which measurable chemical changes are produced by the action of ionizing radiation, offer the best approach to the measurement of integral dosages. Although they are much less sensitive than are ionization methods, they do permit the direct measurement of an average volume dose. A number of chemical dosimeter systems have been and are being investigated for their applicability to this particular problem. Except for phantom spaces immediately adjacent to sources, chemical yields have been found to be too low to permit accurate measurement of doses unless the source size is in the curie-decacurie range or unless the source exposures are made over extended periods of time. The former alternative is undesirable because of health physics hazards and because of cost. The latter alternative would require that the chemical system used be stable over the period of exposure or be susceptible to accurate correction for any such instability. In addition, with studies involving short half-life isotopes there will necessarily be a practical limit on the extent of this exposure period. The frequently employed ferrous and ceric systems have been found to be impractical for low dosage phantom measurements since they both exhibit uncorrectable instabilities in the concentration ranges at which they would have to be employed. The ferrous system is subject to variable autooxidation and the ceric system is subject to photodecomposition. Aqueous benzoic acid solutions, a system suggested by Day and Stein, although less sensitive than other systems, have been found to be quite stable. The Folin phosphotungstic-phosphomolybdic acid method used by Day and Stein for the determination of the hydroxybenzoic acids products has been found to be unreliable. As a consequence a new method for their determination involving their ultraviolet light absorption in alkaline solution has been developed. The yield of mixed hydroxybenzoic acids as determined by this method has been found to be linear with dose. The effect of pH and of concentration of benzoic acid used on the yield has been studied. Although the benzoic acid system is stable with time its sensitivity is such that even with extended periods of source exposure curie size sources would still have to be used. At present it is felt that adequate sensitivity can be achieved with moderate sized sources by concentration of the benzoic acid radiation products through solvent extraction. This is being investigated. One of the difficulties being encountered is the necessary development of another method of analysis, which can be employed in the presence of large amounts of benzoic acid, since the present method is not practical under such conditions. Methods that are currently being investigated for their applicability are Jorissen's test, Millon's reagent, the Theis and Benedict diazo method, and the ferric chloride test. A search is being continued for new and more sensitive chemical dosimeter systems which could be employed in the present work.

B. The problem of dosage from external sources—geometry and dosimetry of rotational teletherapy methods as related to—

1. The shape, volume, and dose of the focal area.
2. The shape, volume, and dose of the entrance and exit sweeps.
3. Total integral dose.
4. The shape of the cutoff area and its dosage profile.

C. Clinical dosimetry and integral dose.

D. Scintiscanner dosimetry and geometry.

E. Isodose lines around organs.

F. Brachytherapy devices.

IV. The Routine Program (Entire Staff)

A. Clinical care of patients—general clinical study of neoplastic diseases.
B. Clinical biochemical studies.
C. Diagnostic hematology and hematologic effects of radiation.
D. Study of techniques of handling isotopes.
E. Health physics.
F. Radioassay of human blood, urine, feces, and tissues.
G. Histopathologic study of neoplastic disease. Autopsy program.
H. Autoradiography.
I. Consultation with visitors.
J. Monday afternoon administrative staff meeting.
K. Thursday evening scientific conference.

V. Training Program (Entire Staff)

A. Residents from medical schools.
B. Residents from Air Force.
C. One-year approved residency in experimental medicine.
D. Instructional participation in regular radioisotope course of training division.
E. Postresident assistantship.
F. Special medical courses (February 1951 and September 1953).

VI. Cooperative Program (Entire Staff)

A. Conferences with medical division consultants.
B. Research participant program.
C. Cooperative research projects.

Dr. Brucer. Before finishing my presentation I would like to call your attention to the exhibit on your right (exhibit 42, p. 75), prepared by the American Museum of Atomic Energy, at Oak Ridge, Tenn.

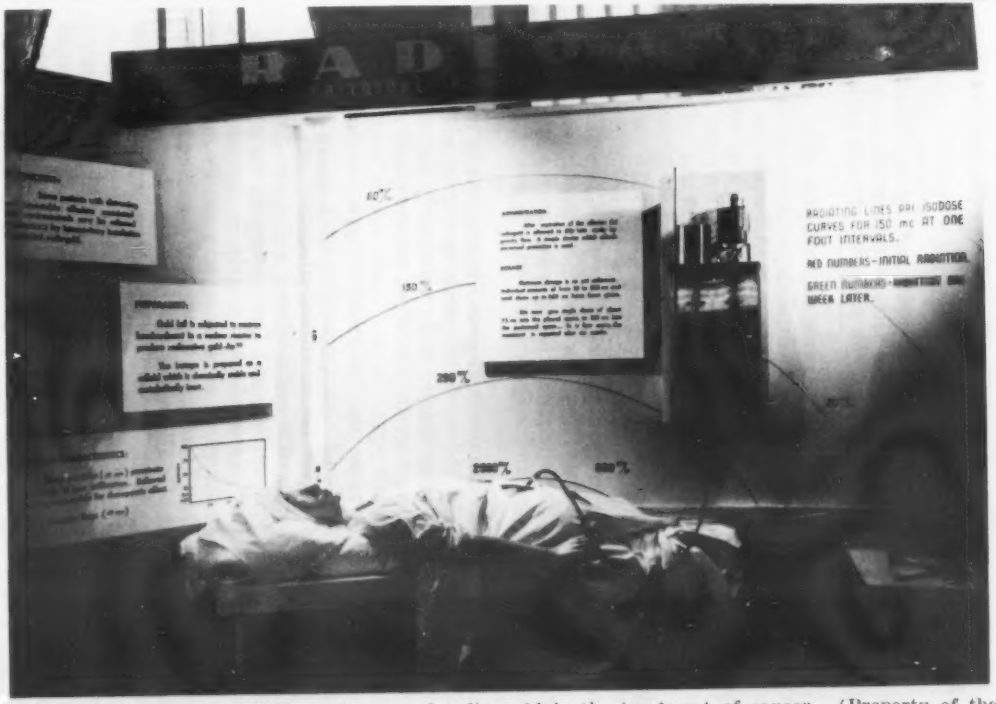


EXHIBIT 42.—Full-scale exhibit of the use of radio gold in the treatment of cancer. (Property of the American Museum of Atomic Energy, Oak Ridge, Tenn.)

Representative HINSHAW. We are very appreciative of your presentation, Dr. Brucer. It opens a new vista, that of teletherapy, and other isotope uses entirely new to medical therapy. And we are very glad to receive the information. We appreciate it very much.

STATEMENT OF DR. LEE EDWARD FARR, CHAIRMAN, DEPARTMENT OF MEDICINE, BROOKHAVEN NATIONAL LABORATORY, UPTON, LONG ISLAND, N. Y.

Representative HINSHAW. The next and last witness today will speak on the use of neutron capture reactions in the treatment of cancer and the use of radioisotopes in the study of chronic kidney and heart disease.

Dr. Lee Edward Farr, who will discuss that subject, is entirely competent, being the chairman of the medical department of the Brookhaven National Laboratory. He was born in Albuquerque, N. Mex., and received the B. S. and M. D. degrees from Yale University. He was for a time associated with the Rockefeller Institute Hospital. Later he was director of research and pediatrician in chief to the Alfred I. du Pont Institute. In World War II, he served as lieutenant commander in the United States Naval Reserve, and with the Office of Scientific Research and Development. He is a member of many medical and scientific bodies, including the Society for Clinical Investigation, the Pediatric Society, the Society for Experimental Pathology, the Society for Experimental Biology, and he is a fellow of the Academy of Pediatrics and a year ago was Sigma Xi national lecturer.

Dr. Farr came to Brookhaven in 1949 and is principally responsible for the development of the medical program there, adapting his knowledge in the field of pediatrics and particularly kidney diseases to the development of the program of medical research built up around the Brookhaven pile.

Dr. Lee Edward Farr, we are delighted to have you and to have your contribution today on this important subject, being the use of neutron capture reactions in the treatment of cancer and the use of radioisotopes in the study of chronic kidney and heart disease.

Dr. FARR. At Brookhaven National Laboratory, in the medical department, we have been interested particularly in the use of radioactive isotopes and machines of nuclear science in developing concepts of disease as well as developing treatments for disease. For, as you know, the concept of a disease is the father to the treatment of that disease. And as our understanding of disease states grows, our effective control of those states will improve.

Now, the research which goes on at Brookhaven in the development of our program is intimately associated with the development of medical research throughout the United States, for we are dependent upon our colleagues in universities and research institutes throughout the country to bring forth new facets of knowledge which may provide us with opportunities further to explore either these facets or related ones by the radioactive isotopes which we may have available to us.

For your edification, I have briefly sketched out on this rather complicated chart (exhibit 43, below) the program which we are presently following at Brookhaven.

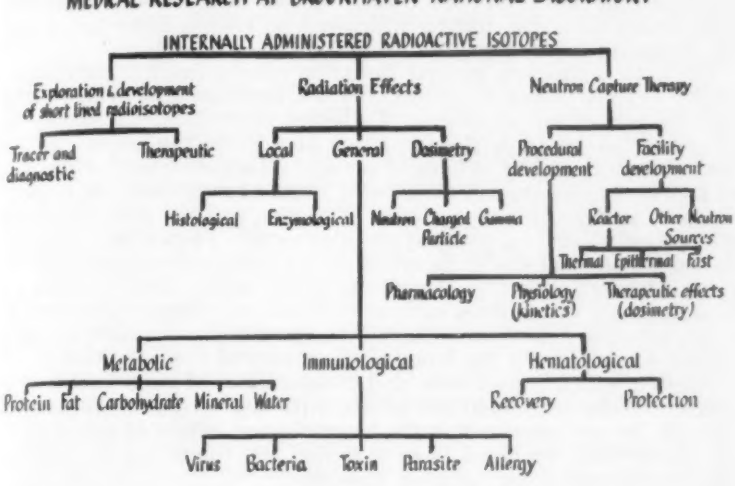


EXHIBIT 43

I should make it very clear that there is no statement made on this chart of the very important part which is played by our colleagues at Brookhaven in the reactor department, the physics department, the chemistry department, the biology and health physics departments there, without whose assistance, of course, we would be unable to carry out our particular part of the program.

At Brookhaven, we have concerned ourselves primarily with what we have called internally administered isotopes; that is, either radioactive isotopes which are radioactive at the time of administration to the individual and by virtue of their passage into the bloodstream and to various parts of the body, give us the knowledge which we seek, or isotopes which can be made radioactive within the body and thereby achieve certain specific effects in disease control which are desired.

Our program is divided into three general parts: (1) The exploitation and development of short-lived radioisotopes, (2) the effects of radiation in man, and (3) neutron capture therapy.

In this first area of short-lived radioisotopes study, we are endeavoring to find what peculiar and advantageous uses may be made of radioactive isotopes which have a short half-life, from a fraction of a second up to perhaps 2 days. In this endeavor, we are exploring a number of these materials, some of which I will mention later.

Secondly, we are, of course, concerned, and very seriously so, with radiation effects on the human being. These can be divided into study of the local effects, the general effects, and dosimetry. By local effects is meant the histological or architectural changes occurring in organs

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or parts of organs as a result of localization of the radioactive isotope therein, and the enzymological changes which may be local or general as a result of the radiation. These latter may not be apparent to the observer who uses a microscope. However, for the chemist and the physician the effects on these enzyme systems may be of even greater significance than the changes which can be readily observed by the eye under the microscope.

We have, under our general radiation effects, again three components: (*a*) the metabolic effects, (*b*) the immunological effects, and (*c*) the hematological effects. To better understand the metabolic effects we are studying the formation of protein, the major constituent of muscle and by volume of bone, the formation and utilization of fats as well as some of the related steroid compounds, the utilization and storage of carbohydrates or sugars, and the distribution of mineral constituents of the body and also water. To gain knowledge of the immunological effects we are studying the effects on resistance to virus infection, to bacterial infection, to toxins, such as diphtheria or tetanus toxin, to parasites such as trichinae, the little worms which infest muscles, and to the allergy type reaction, where there is some altered mechanism in the immune operations of the body that gives a reaction which is undesired and frequently is of considerable discomfort to the individual but seldom with any serious consequences. Thirdly, we are interested in the hematological effects of radiation—the recovery of the blood from radiation and the means whereby it can be protected from radiation damage.

Representative HINSHAW. Doctor, to get back to that subject of allergy, you say that it does not have any particular damaging effects to the human system. I beg to differ with you. I have a very great allergy to poison ivy and poison oak, and if anybody thinks that is not damaging, they had better do my scratching.

Dr. FARR. I have some allergies myself. I can sympathize with you.

To come back to our hematological studies, we are interested in the recovery of the blood from the effects of radiation, and the means whereby the blood can be protected from radiation effects. This is a very important feature, because with specially administered radioisotopes one depends upon the blood to carry the isotopes to the site of action. And unless the blood can be protected from the action of the radioisotope while it is in transit, or immediate recovery from these damaging effects can be assured, there is a definitely limiting factor in the control of some disease states such as thyroid carcinoma.

While these studies are generally concerned with all facets of biological reactions which occur in the human body, the researches are being intensively prosecuted through study and treatment of a relatively few diseases which we are admitting to the Brookhaven National Laboratory Hospital. I have some pictures here of a few representative patients with some of these diseases. We have thyroid cancer, of which you heard earlier this afternoon, from I believe each of the preceding speakers, and of course all of us are interested in effectively bringing these cancerous growths of thyroid under control.

Now, in theory the radioactive iodine isotope I^{131} should provide an ideal means of control of this malignant disease. However, in fact it is found that only about 10 percent of thyroid cancers can in the first place be induced to take up radioactive iodine so that they

may be treated. And furthermore, when the cancer is spread throughout the body in widespread metastases, it is also found that these different tumor growths, which are occurring perhaps in the lung, in the brain, or in the bones, will not of themselves take up radioactive iodine at the same rate or to the same degree at the same time. Therefore, it becomes of great moment to us to determine how these various daughter thyroid cancers can be induced to take up adequate amounts of radioactive iodine and by so doing be destroyed. And this has led us into the field of pituitary-thyroid interrelationships, which occur time and again in various of our studies, because of the great importance of the pituitary in regulating all of the glandular activities of the body. One pituitary hormone which is called thyroid-stimulating hormone is capable of acting either on the normal thyroid gland or on some cancers of the thyroid in such a way that these metastatic cancers will then be induced to take up large quantities of radioactive iodine. When a patient, in such a condition of receptivity, is given iodine 131, it then is possible to give a dose to that metastasis, which in some instances has completely obliterated the metastasis. However, we have not been able to achieve this uniformly throughout the body of any given individual patient. But we have been able, over a period of several years, to keep a number of these patients under rather effective control with repeated doses of radioactive iodine.

Furthermore, this particular disease gives us an opportunity to study the effects of radioactivity on the blood-forming organs and how some of the difficulties that one might normally encounter in the administration of other radioactive isotopes in their passage through the blood can be ameliorated or obviated.

We have found that by a study of these patients, with tracer doses, prior to giving the therapeutic dose, we can in some instances make a quite reasonably accurate prediction as to how much radiation the blood will receive for any given therapeutic dose that we may administer to this patient.

It is obvious that by such means we can skirt that dangerous area where we might give the patient too much radioactivity and destroy his blood-forming organs, at the same time giving him the maximum amount of therapeutic treatment which is possible at that time.

There are some patients in whom we cannot make this prediction, because the behavior of the iodine in the blood is not according to the concepts which we initially held on this, and at the present time we are further exploring this group of patients. Oddly enough, although we at first thought they were in the group that we thought we must list as failures for this particular approach, it now appears that they may be the people most favorably situated for treatment with iodine 131.

We have treated patients with metastatic carcinoma both of prostate and chest.

Representative HINSHAW. Let me interrupt here for the purpose of the laymen who might read the record.

May we have a definition of "metastatic carcinoma" or cancer? That term has been used several times both in your discussion, and I believe in Dr. Brucer's discussion.

Dr. FARR. The cancer arises in one cell of the body, and from this first origination of the cancer it derives its name. For example, if the

cancer begins in the thyroid it is called thyroid cancer, or if in the breast it is called breast cancer, and so on, for the other organs of the body. One of the peculiarities of most cancers is their ability to grow anywhere in the body. If one cell or a few cells of this original cancer find their way into the blood stream or into the lymphatic channels and thereby into the blood stream and are carried to a distant portion of the body and lodged there by virtue of perhaps having become too large to continue to pass through the blood vessels, these daughter cells then can grow and become exactly as the original cancer, but in a remote region of the body. That is, they are daughter cancers arising from some primary source, which in itself may be small, though they may be large. The size of the distant cancer is not related to the size or the type of cell of origin of the original cancer. There is a condition of widespread cancerous growth throughout the body.

Representative HINSHAW. And that is referred to as a metastatic carcinoma?

Dr. FARR. Yes; a cancer which is found in a portion of the body other than at the site of origin.

Representative HINSHAW. That is of a distinctly different type than that which is entirely localized; is that correct?

Dr. FARR. Yes; it is a different type from that which is entirely localized, in that it has potentialities for growth in environments normally considered unfavorable which the localized cancer frequently does not have.

Representative HINSHAW. You speak, for example, of a thyroid carcinoma. Now, that would be in this case a localized affair; would it not?

Dr. FARR. No, sir. The patients whom we are treating with thyroid carcinoma have widespread thyroid cancer in other tissues of the body, such as the lung, the brain, and the bone. If the cancer of the thyroid were limited entirely to the thyroid, in most instances this could be removed by the surgeon completely, and with no further difficulty, as far as that patient is concerned, from that particular cancerous growth. (Exhibit 44, p. 81.)

Representative HINSHAW. Then it, too, is a metastatic cancer.

Dr. FARR. It, too, may be a metastatic cancer.

Representative DURHAM. The metastatic cancer may be either fast-growing or slow-growing?

Dr. FARR. Yes.

Representative HINSHAW. To differentiate metastatic cancer, what would be its, let's say, opposite number, or differentiating type?

Dr. FARR. It is impossible to tell in every instance from looking at a cancer whether it is likely to spread or not. However, experience has told us that certain types of cancer, such as skin cancer, will tend to be localized and grow about the site of the origin, whereas other types of cancer, particularly cancer of the prostate gland, cancer of the breast, and cancer of the thyroid, are particularly liable to have these offshoots or daughter cancers at some distant part of the body.

Representative HINSHAW. What would be the term to be employed as to a type of cancer that is localized, in contradistinction to a metastatic type?

Dr. FARR. We would use the term "cancer in situ," in one place.

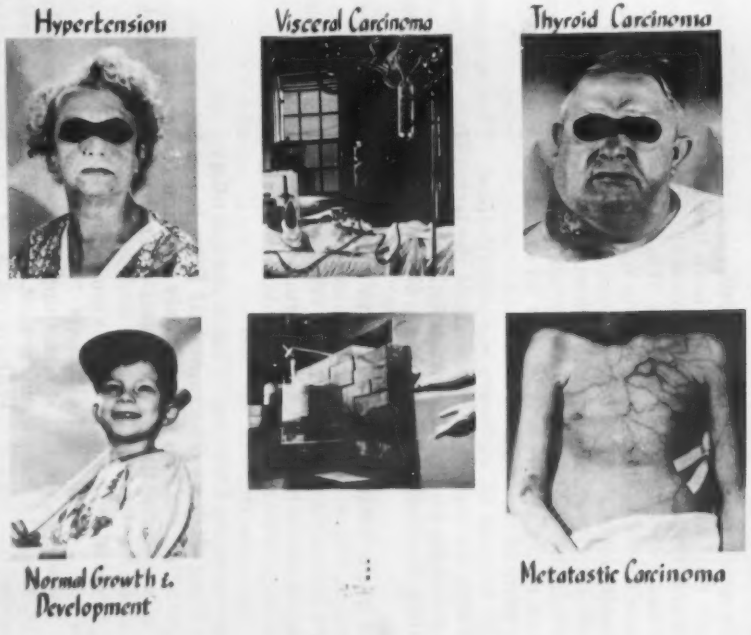
Hypertension
Visceral Carcinoma
Thyroid Carcinoma
Normal Growth & Development
Metatastic Carcinoma

EXHIBIT 44

Representative HINSHAW. Then all you do is use the Latin term?

Dr. FARR. That is correct.

Representative HINSHAW. I can think of some others, but we will not use them here. They might confuse the laymen.

Dr. FARR. Most of the problems in cancer today, I think, arise from the fact that these cancers do spread to remote parts of the body. Where spread does not occur or is very limited our treatment is quite effective by means previously at hand. As a general statement, I think that would be reasonably true.

Representative HINSHAW. You may proceed.

Dr. FARR. Thank you, sir.

In ovarian carcinoma, as Dr. Brucer has told you, there are frequently fluid accumulations. We have treated this not with radioactive gold but with two other isotopes, chlorine 38, which is a short-lived isotope of chlorine having a 37½-minute half life, and with krypton 87. The chlorine 38 is given as ordinary sodium chloride or table salt and is freely soluble throughout all body fluids. However, its radioactivity exists over such a short period of time that it expends practically all of its radiant energy while still within the abdominal or chest cavity and there is little or no radioactivity left to escape to other parts of the body.

With krypton 87, we have a gas which is inert. That is, it will not react with the chemical compounds of the body. It is relatively insoluble in body fluids. And it is admirably constituted for treatment of fluid accumulations in the chest which may be caused by metastatic cancer.

The gas is made in a container in a reactor, then frozen into the solid state, following which, at the time of administration it is warmed up and becomes a gas. Through a suitable tube the gas is channeled through a needle into the chest cavity, which may cause some collapse of the lung, if that has not already occurred from the fluid which has been there recently.

Representative DURHAM. What is the life of it?

Dr. FARR. It has a 78-minute half life. It is a beta emitter, with penetration of the beta particles only a millimeter or so. Thus it is not likely to irradiate any structures other than those to which it is immediately adjacent.

Representative DURHAM. This is something relatively new, is it not, Doctor?

Dr. FARR. Yes, sir. It is something that we have been exploring. We have treated a few patients with it. We still have many problems of this kind to work out. We have not as yet published a report on it.

We also have under study by Dr. Dahl and his group, hypertension, or high blood pressure, which is a disease affecting many people, as you well know. The causes of hypertension are obscure. The treatment of hypertension is unsatisfactory. In recent years, there has been a rather successful attempt made to treat many people with hypertension by limiting the salt in their diet. Patients with high blood pressure on a low salt diet frequently will respond by an alleviation of rather severe damage, for instance, to the retina of the eye and other blood vessels, presumably, in the brain, and become much more normal both in their subjective feelings and in their objective examination.

All people with hypertension do not respond to this low salt diet, and by the use of radioactive sodium we are endeavoring to determine two things. One is whether sodium itself plays any role in the genesis, that is, the production, of hypertension, or whether it plays a significant role in the exacerbation of preexisting hypertension. Also whether by the use of radioactive sodium we could determine over a short period of time whether an individual would respond satisfactorily to the low-salt diet or not.

If this could be ascertained, it would be possible then within a matter of a few days to determine whether this patient would respond to the low-salt diet, although that response itself, when he was placed on the low-salt diet, might take several weeks or even some months to be achieved.

Our results to date are complex. We require a good deal more data before we can analyze them. We have uncovered in these patients a fact which is of considerable interest to those interested in water and salt metabolism, in that the sodium not normally exchangeable in the body may become responsive under some conditions so that this sodium becomes generally exchangeable or available for body uses.

It would appear that in some situations, at least in the patients that we have studied with hypertension, a considerable fraction of this hitherto inexchangeable sodium has become exchangeable and is partaking in some manner as yet unknown in the normal vital processes of that individual. We do not know the significance of it in the hypertensive individual at the present time.

Representative DURHAM. How is that administered, Doctor?

Dr. FARR. Any of these isotopes can be given by mouth as a drink or can be injected intravenously. The latter is done when very accurate doses are desired for measuring what we call the sodium space, which is at times a measure of the body water not contained within the cells of the body. This is the fraction which is concerned with swelling, as one ordinarily sees it. Radioactive sodium is also injected for measuring the total amount of sodium in the body. In those two instances we want to know very accurately how much sodium has been given, so that we can then calculate how much water that sodium is dissolved in, or how much sodium there is in the body as a whole.

There is one other thing that I want to pass on briefly, and that is that when you go to your physician he may tell you you are not sick. But there are few, if any, criteria for health. In general these are negative rather than positive. By the study of amino acids with carbon 14, and their incorporation into protein we hope eventually to get some data which may provide more positive data for health rather than merely the absence of disease, as well as correlate this with radiation effects.

There is a disease of young children called nephrosis (exhibit 45, p. 85) which is characterized by an extreme degree of swelling of the body, as you can see in the center panel and in the pictures of these patients at the time of admission to the hospital.

This is a disease which, while one might characterize it as uncommon, is not rare. There are several thousand children suffering from this disease in the United States at all times.

The particular importance of this disease is that it has within it disturbances of protein metabolism, of water and salt metabolism, as is so evident by the swelling, of fat metabolism, of glandular disturbances, and of almost all types of metabolic disorders which one many encounter in a great number of diseases.

We are therefore endeavoring to study this disorder by all the isotopes which we can safely use in such patients in order to gain more insight into the degree of malnutrition which may be present, the steps which may be taken to correct this malnutrition, what measures may be taken to correct the swelling, which is such a prominent and crippling feature of the disease, and what if anything may be done to insure recovery from the disease, which still carries mortality, today, of over 50 percent.

You can see in these pictures how swollen this child is on admission, and from the picture of the same child shortly after the delivery of most of his edema, you can get some idea of the wasting of muscles which occurs in this disease but which is completely obscured by the swelling.

The other four pictures are serial pictures of another patient, the last one taken 3 years after admission. He is now, as far as we can tell, a completely normal, healthy child who has a normal life expectancy.

Now, the cause of this swelling is not entirely understood, and through the use of sodium, potassium, chlorine, bromine, as well as other compounds which are available to us to study body water, we have been studying the kinetics or rates of movement of these compounds through the blood stream into these swollen areas and also the rates of movement from the swollen areas back into the blood stream, in order to try to gain some better knowledge as to the cause of edema and the means whereby it may be brought under control.

The rates of movement of these isotopes can be studied in these large accumulations of swelling, such as one sees in these patients, because a reasonable amount of time is required for any significant amount of the isotope to pass from the blood into the abdominal cavity, which may be full of fluid, or into the legs, which may be markedly distended with fluid. And from these data we are able to derive descriptive equations which mathematically tell us how these isotopes might be expected to behave in the normal individual, and at what rate they might pass through any given tissue. Not because the isotope has a specific affinity for that tissue but because of the nature of the circulation and the water content of that tissue each compound will enter it at some characteristic rate.

And if we can predict this in advance, we then know at what time a maximum concentration of that isotope will be present in that tissue.

Partly as a result of our studies of these nephrotic children, we came to a working hypothesis for neutron therapy which has been used at Brookhaven now for about 2½ years in the treatment of one type of brain tumor that is called glioblastoma multiforme. All types of brain tumor do not have the same behavior, and there are many different kinds of tumor of the brain.

Earlier you asked me about metastases. Brain tumor is one kind of tumor that seldom metastasizes. That is, it seldom if ever grows

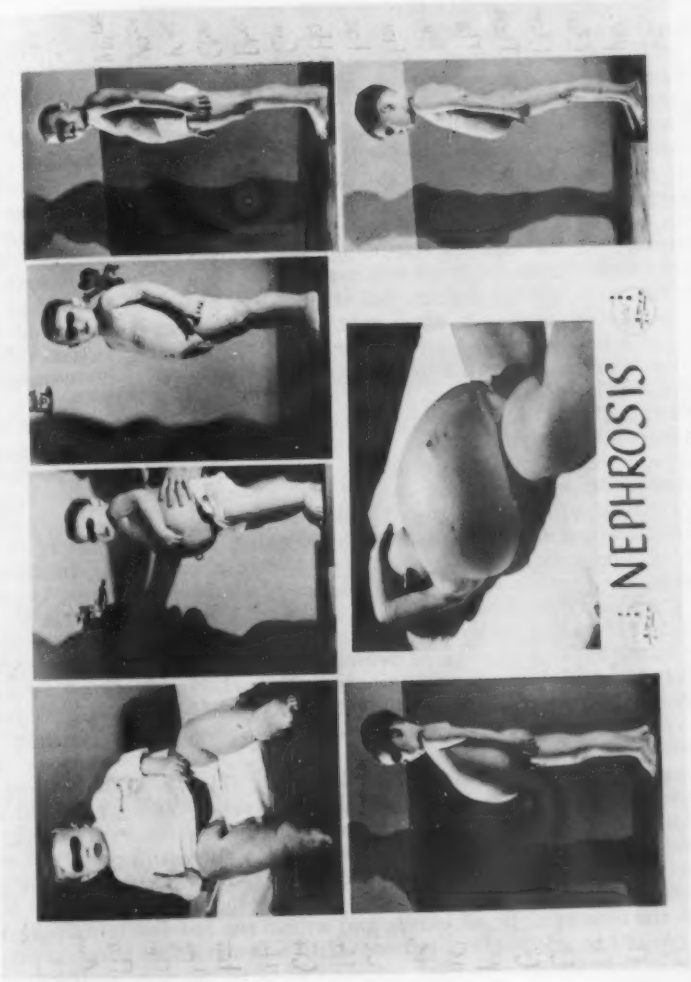

EXHIBIT 45

in any other portion of the body than the brain. However, it may and not infrequently does grow in more than one region of the brain perhaps almost simultaneously.

Glioblastoma multiforme is a uniformly fatal disease with a probable life expectancy of 1 year regardless of the surgical procedure that has been carried out. That is, whether the surgeon has excised or cut out as much of the tumor as he could see and as much of the normal brain surrounding it as dared, or has left the tumor almost as he found it as he goes into the operation, there is little statistical difference in the group life expectancy. However, there may be large difference in the behavior of the patients so treated.

Furthermore, the brain behaves rather peculiarly among all body tissues in that most substances will not leave the blood stream readily as it courses through the brain, whereas in the muscles these substances will leave very promptly. This has been termed the blood-brain barrier. This barrier does not exist in brain-tumor tissue. Therefore, if we inject a compound such as we have used into the blood stream, this compound will rapidly pass out of the blood stream into the water of the tumor, but it does not pass into the water of the normal brain at the same rate. Therefore, for some period of time, as a matter of fact some 60 or 70 minutes after injection, there will be a much larger concentration of this compound in the tumor than exists in the normal brain.

Now, if at this time we subject that region of the body to a stream of thermoneutrons, and if in this compound we have a capture element isotope, boron 10, the boron in the tumor will capture the thermal neutrons, become radioactive, and almost instantaneously disintegrate into an alpha particle and a lithium particle. These 2 particles travel in opposite directions, much as going to the 2 ends of this pointer, and each travels a distance of only about 1 cell diameter. That is, the particle travels the distance of about 8 to 10 microns, or the distance equivalent to the diameter of 1 red blood cell. This means that radioactivity will be limited to the site of origin. So that if the capture isotope of boron exists only in the tumor, which collects it by biological discrimination, then the interaction between the boron and the neutrons will result in a significant radiation to the tumor and no significant radiation to the surrounding normal brain structures.

You see here some pictures (exhibit 46, p. 87) of the first patients that were treated at the reactor at Brookhaven. We have treated a total of 14 patients now. The first five patients received a single treatment. The second 5 patients received up to 4 treatments. And at that time it became evident that our neutron source was not sufficiently powerful. So we spent approximately a year in redesigning the facility on the reactor at Brookhaven, and within the last few months have now treated an additional 4 patients with a neutron flux which is over 10 times that which was used earlier. That is, we now, in the same period of time, apply 10 times as many neutrons throughout the tumor as we were able to do a year ago. It is too early to tell the results of this treatment. We have had some clinical responses which have been very encouraging. We have many, many problems yet to unravel in the general field of kinetics before we can accurately describe the limitations and the capacities of this treatment. But we are encouraged as far as we have gone that it may at some time be useful in the control of these very malignant disease states.

EXHIBIT 46

Representative HINSHAW. You are making very great progress, Doctor. I not only offer my congratulations but those of the entire committee, and I suspect the Congress and the people, for the fine work you are doing at Brookhaven Laboratory, you and your colleagues.

We have heard from the agricultural gentlemen a few weeks ago, and it has been my personal desire to go out on Long Island and visit Brookhaven, but that has been impossible thus far. I understand that certain members of the committee have visited your laboratory and witnessed this particular operation, that is, operation in the sense of something doing, and have been very much amazed at the relief that the patients exhibited. I understand that it is not permanent, but on the other hand it has been a great help. And it shows the pathway toward some future time when we may be able to conquer such things.

Dr. FARR. Thank you, sir. We hope you visit Brookhaven soon.

Representative DURHAM. I also congratulate you, and I would like to ask you a question or two on that.

Have you gone far enough yet to say that you have prolonged life? Of course, we all know it is usually around 6 to 12 months in a brain tumor. Have you gone far enough yet on that?

Dr. FARR. We have no patients who have statistically survived beyond any expected survival time of this disease. On the other hand, we have had patients whose individual survival capacity was believed to be considerably less than the year I mentioned. Some of those patients have survived in reasonably good activity, that is, able to carry on normal social intercourse, to carry on with their family responsibilities, for a period as long as 7 months after beginning treatment beyond their expected life span.

Representative DURHAM. Does it seem to retard the growth of it?

Dr. FARR. It apparently has retarded the growth of the tumor. The patients who are now under treatment we hope will prove to be successful examples of this, but they have only gone approximately 2 months, and certainly no statement can be made as yet regarding them.

Representative DURHAM. I imagine you could observe that very readily, because of the fact that the swelling is very definite and it usually grows very fast.

Dr. FARR. Well, sir, in this particular patient, as you can see, there was a large protrusion. His head was increasing in circumference at approximately a centimeter a day prior to treatment. He was in our first series. The patient's condition became so serious that we did not expect him to survive an additional week. And with excellent cooperation from all our colleagues throughout the laboratory, we were able to synthesize the boron compound and give it to this man a week prior to the time originally scheduled.

This picture was taken some 4 months afterward, at which time he was ambulatory and had returned to his home at Boston.

Representative DURHAM. Of course, if you could get more neutrons into this tumor, wherever it is, by some means you could get a better result.

Dr. FARR. We have two problems, sir. One is to get more neutrons. We think that probably we should have about 10 times as many neutrons as we have at the present time for effective therapy. And the

other is the accessibility of the reactor for the positioning, the proper positioning, of these patients, and the carrying out of the run.

There is also the problem of the administration of capture compounds. Boron has been considered certainly a toxic compound. We are actively engaged in the study of the pharmacology of it. And I may say that some of our patients have had doses of boron which are far in excess of what I, for one, would ever have believed possible 2 years or 3 years ago.

So that we are at the present time increasing the dosage of boron. We have increased our neutrons 10 times over the initial series in flux, but our calculations suggest that we should have another 10 times in order to have at least a condition which would provide sufficient neutrons to bring this tumor under control wherever it might be within the brain cavity.

Representative DURHAM. You would have the trouble, of course, of getting the boron into the patient without producing toxic results.

Dr. FARR. Yes. We think we are making progress in this.

Representative HINSHAW. There is also a problem, I understand, of the neutron source. If they had the medical type reactor that they have been talking about, perhaps they could do even more than they are now doing. Is that correct?

Dr. FARR. I believe there is no question that a medical reactor would permit us to treat these patients and to investigate this approach much more effectively than we can do at the present time.

We are in much the same position as if we were using the Brookhaven reactor for a prototype powerplant. One can do that, but for the best results one uses the reactor designed for the purposes for which it is going to be used.

Representative DURHAM. Then you have a two-way problem instead of a one-way problem. I undersood you to say the primary problem was getting the boron into a position where it would absorb the neutron, not the difficulty of putting in the neutrons.

Dr. FARR. We have the problem of the neutrons. The neutrons are quite different from gamma or X-ray radiation, which will penetrate, in that neutrons are absorbed by body tissues as they come in. So, as they penetrate in depth from the side of the head to the midline the number of neutrons falls off very significantly. This means that we have to have a large number entering the side of the head in order to have a sufficient number in the middle of the head, to do the job that we want done.

Representative DURHAM. Have you tried it on any other part of the body?

Dr. FARR. No, sir. Theoretically it is applicable to some other portions of the body, but we feel that we will gain as much knowledge at the present time by confining our studies to the brain tumors as we would by exploring some of these other malignancies at this time.

Representative DURHAM. But you have gone far enough with it so that you feel it has had some results?

Dr. FARR. Yes, sir. We feel that we have had some results. They have been clinically encouraging. They have not been what we would like to have. We hope that our present series will show the kind of results we think we can obtain with this approach.

Representative DURHAM. Your pathological examination should show after the patient dies, some results.

Dr. FARR. Yes. We have sent some sections to pathologists who were interested particularly in radiation in the central nervous system, particularly to the University of Illinois. They have been very encouraging in their analysis of these specimens. But certainly by examination of them one realizes that an inadequate amount of radiation must provide less than satisfactory results.

Representative DURHAM. That is a pathologist's opinion?

Dr. FARR. Yes, sir.

Representative DURHAM. Thank you very much. That is very interesting.

Representative HINSHAW. Doctor, we appreciate your coming down here and expounding on this work you have been doing. It undoubtedly will be heard around the world, as will all of this testimony today, and although we may seem to be a few in numbers at present, the balance of the committee is engaged in a further undertaking, as you know, and it was not expected that they would be so engaged at the time we scheduled these hearings. Nevertheless, while it is less important that we hear what you may have to say, it is most important that the collation be printed and distributed. And we thank you very much, as do your future readers.

Representative DURHAM. I would like to ask one further question, Mr. Chairman.

Due to the importance of this field of work at the present time, may I ask: Is there any lack of cooperation at the Federal level or otherwise that is hampering your research work at the present time?

Dr. FARR. No, sir. We have the enthusiastic cooperation of every party we have asked to aid us in any way in our venture.

Representative DURHAM. Could you do more if you had more scientific personnel, do you think?

Dr. FARR. I do not believe that we could do more at this time with more scientific personnel. We could increase the rate at which we develop certain aspects of this, but the development is largely dependent upon the production of concepts and the development of basic science. This is difficult to increase by simply increasing the numbers of people involved.

Representative DURHAM. It is not a lack of money?

Dr. FARR. No, sir. There has been no lack of money. We have a group that are slowly becoming thoroughly versed in this approach, and it has taken, I have learned by experience, about 3 years for a physician in our environment before he can integrate these experiences into his ordinary medical thinking. This has been simply the delay of maturation. That is the chief problem which we have encountered, and I know of no way of circumventing this.

Representative DURHAM. Then it is a matter of hard work and slow results?

Dr. FARR. Hard work and slow results.

Representative DURHAM. We here on this level want to give all the cooperation we possibly can in securing funds or whatever is necessary.

Mr. FARR. We are most happy that our colleagues of other universities are able to come to Brookhaven and to spend time with us, partly on their studies and partly on ours, in areas of mutual interest. I

did not have a chance to tell you about our work with xenon, with the State University of Iowa group, who are exploring it as an anesthetic in man and wished to have some specific knowledge of its locus of action, the place of action, on this isotope.

We made the radioactive xenon. We were interested in radioactive gases. We and they learned a great deal from this cooperative study. They have made three visits now to Brookhaven for collaborative studies.

I simply cite this as one of the many instances of collaboration which we have been able to carry on with the universities and medical research institutes and hospitals throughout the country. And we are indeed appreciative that we can do this.

Representative DURHAM. We have, I believe, four such laboratories at the present time under this program that are primarily concerned with the cancer problem. And I am certainly proud of the work that is being done by Commission personnel in cooperation with the universities. I think it is a problem we simply have to lick at some time, at some stage.

Dr. FARR. Yes, sir, and we shall.

Representative HINSHAW. The associated universities, which operate through an association, the Brookhaven National Laboratory, are what?

Dr. FARR. Massachusetts Institute of Technology, Harvard, Yale, Cornell, Columbia, Princeton, Pennsylvania, Hopkins, and the University of Rochester.

Representative HINSHAW. Those are all north and east of Baltimore?

Dr. FARR. They are all in the northeast area of the United States.

Representative HINSHAW. I presume, however, from your statement, that other universities in the Middle West and South have the facilities available to them. You mentioned the University of Iowa at Iowa City.

Representative DURHAM. You have a comparable thing in the South, the Oak Ridge Institute. That has practically the same organization.

Representative HINSHAW. I do not want to put you on the spot, but would you think that this would be a good time, or some near future time would be a good time, to consider the establishment of a medical reactor for the use of the associated universities at Brookhaven?

Dr. FARR. Yes, sir. I think that we have sufficient experience now to justify such a venture, and that if we did have the opportunity of developing a medical reactor, we could speed this work very materially by virtue of the physical plant having been designed for the purpose for which it was being used.

Representative DURHAM. I have been thinking of it in a little broader terms than that, Doctor; establishing a series of them around over the country, if they have been proven to the point where they are worthwhile, for research in the other sections of the country, whereby we can expedite this thing, rather than limiting it to any part of the country.

Dr. FARR. It should not be limited to any part of the country, and there are other areas, notably the University of California of Los Angeles, that are interested in this whole program, and we certainly would like to see them participate with us in solving these problems.

Representative HINSHAW. We are getting to the point now of establishing these medical reactors. And, of course, somebody has to set out the program of how many of them could be profitably used in the United States, that is, profitably from the standpoint of possible results. There ought to be some sort of a maximum number or minimum number that one could establish, or an optimum number, let us say, and thus arrive at the answers to these questions a little sooner than otherwise might be done, possibly prolonging life a few more years on the average. We have prolonged it some 10 years over the last 25.

We thank you very much, Doctor, for your appearance here today, and we only wish that more of us could be present to hear what you have to say. But we assure you that a great many more will read and study the statement you have made.

Dr. FARR. Thank you.

Representative HINSHAW. The hearing is adjourned until 2 o'clock tomorrow.

(Whereupon, at 5:10 p. m., Wednesday, June 2, 1954, the hearing was adjourned until 2 p. m., Thursday, June 3, 1954.)

THE CONTRIBUTION OF ATOMIC ENERGY TO MEDICINE

THURSDAY, JUNE 3, 1954

CONGRESS OF THE UNITED STATES,
JOINT COMMITTEE ON ATOMIC ENERGY,
SUBCOMMITTEE ON RESEARCH AND DEVELOPMENT.
Washington, D. C.

The subcommittee met, pursuant to recess, at 2 p. m., in the caucus room, Old House Office Building, Hon. Carl Hinshaw (chairman of the subcommittee) presiding.

Present: Representative Hinshaw (presiding).

Professional staff member: Edward L. Heller.

Representative HINSHAW. The committee will come to order.

This is a continuation of the hearings begun on yesterday of the Subcommittee on Research and Development of the Joint Committee on Atomic Energy; in which the subcommittee is holding hearings and compiling a record on the contributions of atomic energy to medical research and medical therapy.

STATEMENT OF DR. ROBERT J. HASTERLIK, ASSOCIATE DIRECTOR, ARGONNE CANCER RESEARCH HOSPITAL, CHICAGO, ILL.

Representative HINSHAW. The first witness today will be Dr. Robert Hasterlik, associate director, Argonne Cancer Research Hospital, Chicago, Ill., who will speak on the subject of the Medical Implications of Spleen Shielding as a Means of Reducing Whole Body Radiation Injury, the Argonne Cancer Research Hospital Cobalt Rotational Teletherapy Unit, and Radiothulium Portable X-Ray Equipment.

Dr. Hasterlik was born in Chicago, Ill. He received his bachelor of science degree at the University of Chicago and his doctorate of medicine from Rush Medical College of the University of Chicago.

Dr. Hasterlik was a lieutenant commander in the United States Navy Medical Corps from 1942 to 1946. After World War II he taught at Northwestern University Medical School. He went to the University of Chicago as assistant professor of medicine, and to head up the health program for the Argonne National Laboratory, and is now associate professor of medicine and associate director of the Argonne Cancer Research Hospital.

Dr. Hasterlik is a member of a number of scientific societies. He has made important contributions to the field of radiation medicine, especially with studies of persons who were given radium therapeutically.

Dr. Robert J. Hasterlik, we are delighted to have you present to contribute to this symposium.

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Dr. HASTERLIK. Thank you very much, Mr. Chairman.

I am going to try to cover essentially three of our projects at the Argonne Cancer Research Hospital, which is operated by the University of Chicago for the Atomic Energy Commission.

The first field is the special research interest of Dr. Leon Jacobson, who is the director of the hospital.

In the early days of the Manhattan project, when studies were being done on the toxicity of the various radio elements, Dr. Jacobson carried out some studies on the toxicity of strontium 89 and strontium 90 injected into mice. These studies indicated that although the animals died a radiation death, in many cases the bone marrow had to a great extent regenerated.

In an analysis of these results, it became apparent that the strontium had been deposited mainly in the bone as one of the bone-seeking elements, and only to a very slight degree in the spleen. This led Dr. Jacobson to surmise that in some way perhaps the presence of a relatively undamaged spleen, in the animal, led to a regeneration of the bone marrow.

It then became apparent that further work would have to be done on the relationship of the spleen to the control of blood formation.

It became apparent that whole body irradiation leads to widespread tissue damage, and death may be related to the damage of one or more organ systems; but destruction and delayed recovery of blood-forming tissue is considered to be one of the most critical.

Dr. Jacobson devised a means of separating the effects of irradiation on the spleen from the effects of irradiation on the total body. And what he did was this:

The small mouse to be irradiated is operated upon surgically under anesthesia, and the spleen is brought outside the body. The spleen is then shielded by a small lead shield, and the entire animal is irradiated.

The total animal is irradiated, but the spleen is spared irradiation.

It is known that if one gives a certain radiation dosage to a group of mice, a certain number will die. There will be a certain percent mortality. And using a radiation dose that was expected to be lethal in most of the mice, Dr. Jacobson found these very interesting results: That if as a control the kidney was shielded, the same number died as if the whole animal had been irradiated, and if a leg were shielded, slightly less, but still most, died. But if the spleen were shielded, only 20 percent died out of an expected 100 percent mortality.

It was also found that in these experiments that in the irradiated control, that is, the animal who has his entire body irradiated, the white cell count fell precipitously to less than 500 cells per cubic centimeter. If the spleen were shielded, then the blood count fell initially at the same rate as if it had not been shielded, but it recovered rapidly, so that after a period of time it was essentially the same as in the control that was not irradiated.

Representative HINSHAW. You gave those mice a dose of a thousand roentgens, which is twice what is ordinarily considered a lethal dose for humans?

Dr. HASTERLIK. Correct; and that is not quite twice for the mouse.

Representative HINSHAW. The same amount, but you had 20 percent casualties, as against an expected 100 percent?

Dr. HASTERLIK. Correct.

Representative HINSHAW. What do you ascribe that to?

Dr. HASTERLIK. One of the factors concerned in death is destruction of the bone marrow. These animals had a wiping clean, as it were, of the bone marrow of normal cells, but if the spleen were shielded the bone marrow recovered so that it appeared normal within 8 days. In other words, spleen shielding somehow aids recovery of the bone marrow and reduces this cause as a factor in radiation mortality.

Representative HINSHAW. So there is a direct connection of some sort between bone marrow and spleen. We do not know yet what it is, I take it?

Dr. HASTERLIK. That is right.

Now, further studies were done to demonstrate the length of time that it was necessary that the spleen be left in circulation after irradiation of the spleen shielded animal in order to cause a regenerative effect on the bone marrow.

In one study the mouse had his spleen exteriorized and shielded during irradiation, and then the spleen was surgically removed from the animal at different intervals of time; at 15 minutes, 30 minutes, 1 day, and 3 days. If the spleen was only left in the circulation for 15 minutes after irradiation, 75 percent mortality occurred. If the spleen was left in 30 minutes, there was a reduction in the mortality to 66 percent. If it was left in 1 hour, there occurred a very marked reduction, to approximately 22 percent. There was not much gained in reduction in mortality by leaving it in up to 3 days. In other words, during the 1 hour that the spleen remained in the circulation after irradiation, something happened, and the circulation through the unirradiated, shielded spleen aided the recovery of the bone marrow. And this effect took place during 1 hour.

Here again, if the spleen were left in place for 1 hour, the results were almost as good as if the spleen was left in indefinitely. The rapidity of the recovery of the bone marrow, however, is related to the length of time the originally shielded spleen was left intact in the circulation.

These and other facts we have talked about tend to indicate that survival may not be wholly dependent on blood recovery. In other words, there are other factors concerned.

Spleen-shielding or post-irradiation measures, such as the injection of spleen cells, cells from the mouse or of bone marrow from other species or ground up spleen tissue or ground up embryo tissue, increased the percent survival and hastened the recovery of blood-forming tissues.

One can give a lethal dose of irradiation to the mouse and give an almost mid-lethal dose of irradiation to the spleen at the same time, but if there is a differential there will be recovery, even though the irradiation to the spleen is almost in the midlethal range.

One of the other factors concerned with survival——

Representative HINSHAW. Are you going to tell us some time what your ideas may be as to the conclusions that ought to be drawn from this?

Dr. HASTERLIK. Yes.

Representative HINSHAW. Is that coming now, or later?

Dr. HASTERLIK. Yes. This will come shortly after I finish a discussion of some of the effects.

The shielding of the spleen has an effect upon the formation of antibodies, which are also important in the recovery from radiation effects by aiding in the control of infection.

It was found that the intravenous or intraperitoneal injections of less than 5 milligrams of washed spleen cells, spleen homogenates, bone marrow, or embryo homogenates, will increase the survival of mice exposed to lethal doses of irradiation.

These materials may be given as late as the second or fifth day after irradiation.

A very important fact is that the injection of rat bone marrow into irradiated mice will effectively increase survival.

The studies on the injection of rat bone marrow were first carried out by the late Dr. Egon Lorenz at the National Institutes of Health and were confirmed by Dr. Jacobson. This is a very important point, because here we have cells from an entirely different species of animal protecting another species. I will refer back to that in a moment.

Bone marrow of mice or rats, in the mouse lends a factor which aids in the recovery of the bone marrow. If bone marrow is given after a lethal dose of radiation, the reticulocyte count jumps at the 16th day to a very high level, indicating that a rapid recovery of the bone marrow is occurring.

Representative HINSHAW. That is a different species, but it is not of a different family.

Dr. HASTERLIK. But there is enough species specificity between the rat and the mouse from all we know biologically to indicate that the rat cells should not survive in the mouse. The cell should die in an animal of another species. And I will refer to that.

Now, one of the implications of the studies using rat cells in the mouse is that this is not a seeding of normal cells into the bone marrow, with a regrowth of these cells. It would tend to imply that a substance is formed in the spleen, as rapidly as during the first hour after radiation, which can cause a recovery of the bone marrow, and that this is possibly a chemical substance produced either in the nucleus of the cell or in some part of the cell; because it would appear that ground-up cells in which, as far as can be determined, there are no intact cells, can cause some recovery of the bone marrow from irradiation damage, and lower mortality.

There are as yet no practical applications of these studies. But this work elucidates some very interesting and fundamental mechanisms. It helps us to understand at least one of the mechanisms which has to do with the control of blood formation.

Another interesting observation of Dr. Lorenz is that in a certain strain of mouse it is a fact that if these animals are irradiated with a high level of irradiation, a very high percentage of the animals will develop leukemia. If they are irradiated with the spleen shielded, the expected percentage of leukemia does not develop. This is interpreted as an indication that something in the spleen or spleen cells produces a substance which helps regulate the normal recovery of the bone marrow.

In summary, these studies make it apparent that a substance or substances may be found which can reverse some, but not all, of the deleterious effects of external radiation after the radiation has been delivered.

I see I am listed to demonstrate two of the other projects of the Argonne Cancer Research Hospital at the University of Chicago.

This is a photograph of our cobalt 60 rotational therapy unit (exhibit 47, below).

This is a photograph of the actual cobalt source (exhibit 48, p. 98). It is a cylinder 7 millimeters in diameter and 2½ inches long. It weighs only 10 grams. But yet when it is irradiated in the materials testing reactor, as our sources are, it will become 1,800 curies of radioactivity, which is the equivalent of 4 pounds of radium.

Representative HINSHAW. What is the half life of cobalt?

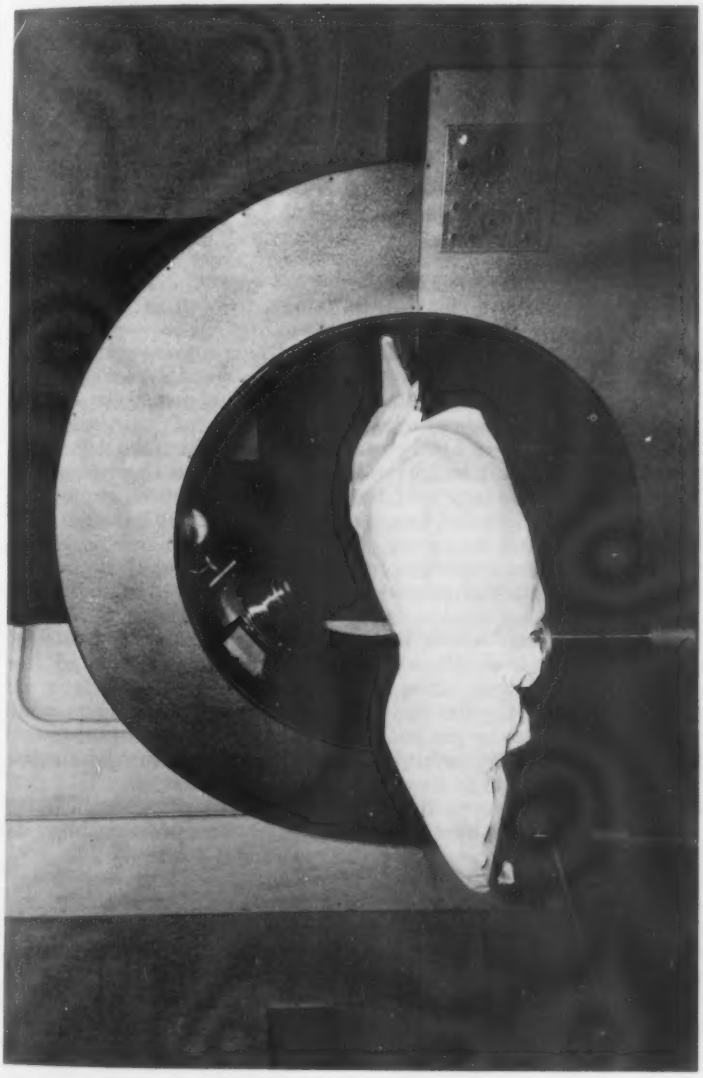

EXHIBIT 47.—Cobalt 60 rotational therapy unit.

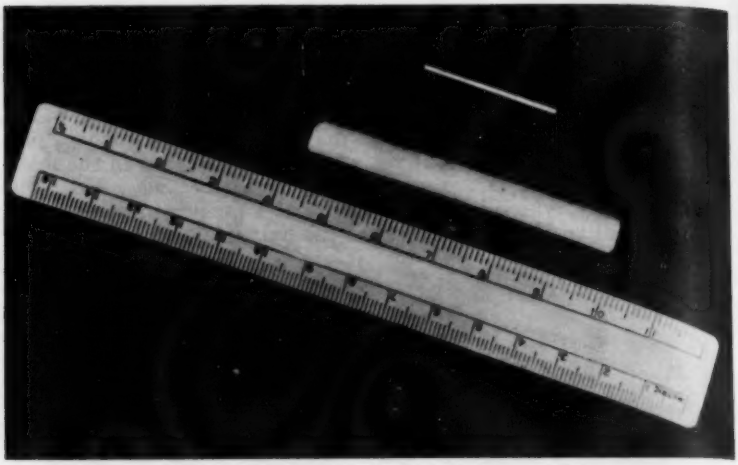

EXHIBIT 48.—Photograph of the actual radio cobalt source for the Argonne Cancer Research Hospital for the teletherapy unit.

Dr. HASTERLIK. It is 5.2 years. We expect that we will have to replace our source about every 2 to 3 years, to keep us in the range of a decently short patient treatment time.

One of the other interesting features of this machine is that the shield for the cobalt is made of uranium. The interesting thing about this is that since uranium is a very dense metal, we can get away with only 950 pounds of uranium as a shield. If this were lead, it would weigh more than 3,000 pounds, which would make it mechanically extremely difficult to rotate the source around the patient.

The advantage of rotation of the source of radiation around the patient is that the patient is placed, as you see there, with the patient's tumor at the center of the circle. And as the source rotates around the patient, the tumor is always in the center of irradiation, but the skin and surrounding tissues are only being irradiated a small fraction of the time.

One of the most troublesome limiting factors in radiation treatment in the past has been that although it was possible to put a lethal dose of radiation into a deep tumor, one very often destroyed so much normal tissue, especially the skin, that it was impossible to complete the therapy or to save the patient's life.

This is a very interesting and very helpful application of the use of uranium as a shield.

Representative HINSHAW. As I understand it, uranium, as such, the normal uranium cannot be sold to hospitals at the present time. Is that right?

Dr. HASTERLIK. That is my understanding.

Representative HINSHAW. And therefore the supply of this equipment is limited to authority of the Atomic Energy Commission exclusively in the ownership of the material. It is merely a loan. Correct?

Dr. HASTERLIK. Correct. Our hospital is part of the Atomic Energy Commission, and the material is on loan. It is not our property.

Representative HINSHAW. It would take an amendment to the law to permit hospitals, the ordinary run of hospitals, to acquire such a machine?

Dr. HASTERLIK. Yes; that is my understanding. They could not under the present law.

Representative HINSHAW. Could they lease the equipment?

Dr. HASTERLIK. That I don't know.

Representative HINSHAW. I rather doubt that, myself.

Dr. HASTERLIK. This unit was designed as an experimental unit to test the efficiency of a very small source rotating around the patient. From preliminary studies—and we have been using this apparatus for approximately 4 months now—it looks exceptionally promising. It is possible to put a very large amount of radiation into the patient with a minimum of damage to the patient's other organs.

Representative HINSHAW. You could rotate that around another axis also, if you wanted to, that is, a vertical axis or any other axis out of the plane of the perpendicular to the body?

Dr. HASTERLIK. Correct. This design was chosen because it makes it possible for the patient to be recumbent upon the table during treatment, and many sick patients cannot stand up or sit up. We chose this design so that the patient could be recumbent with the source rotating around him. Although, it doesn't on this model, the head angulates out to 45 degrees, so that we can cut conical sections. For instance, if one wishes to treat a brain tumor, the patient is placed at the extremity of the table and with angulation of the head of the unit to 45 degrees, the beam of radiation shines into the head from the end and puts in a cone of radiation with the tumor at the apex.

Representative HINSHAW. You could accomplish a similar effect by rotating the platform on which the patient is lying in a horizontal plane for a matter of 45 degrees also.

Dr. HASTERLIK. Correct. Actually, the table goes up and down and moves in and out. So we have three degrees of freedom of the table. The unit also rotates either clockwise or counterclockwise, and one can chose any sector. For instance, if one wishes to spare the spinal cord in certain treatment, the unit will rotate from approximately, let us say, 75 degrees, around to the other side, 75 degrees, back and forth, omitting the posterior surface. We have considerable flexibility in this unit.

One of the other projects that we have under way is the development of a source of radiation for clinical radiography. Approximately 2 years ago, Professor Mayneord, in England, pointed out that thulium, which is element No. 69, when irradiated, gave off radiations which were in the range of the radiations given off by conventional X-ray tubes. In England at the time, the requisite flux was not available for producing thulium of a very high specific activity. However, it came to my attention not long ago through Dr. Samuel Untermyer, of the Argonne National laboratory, that sources of high specific activity thulium were available.

The thulium 170 unit gives off two gamma rays. One comes from the daughter of thulium, which is ytterbium, and that is of 52,000 volts energy. The thulium itself gives off a gamma ray of approximately 82,000 volts. This is right in the range of the energies that are given off by the usual X-ray radiographic unit.

If you would like, I will demonstrate such a unit (exhibit 49, below) pointing out its advantages.

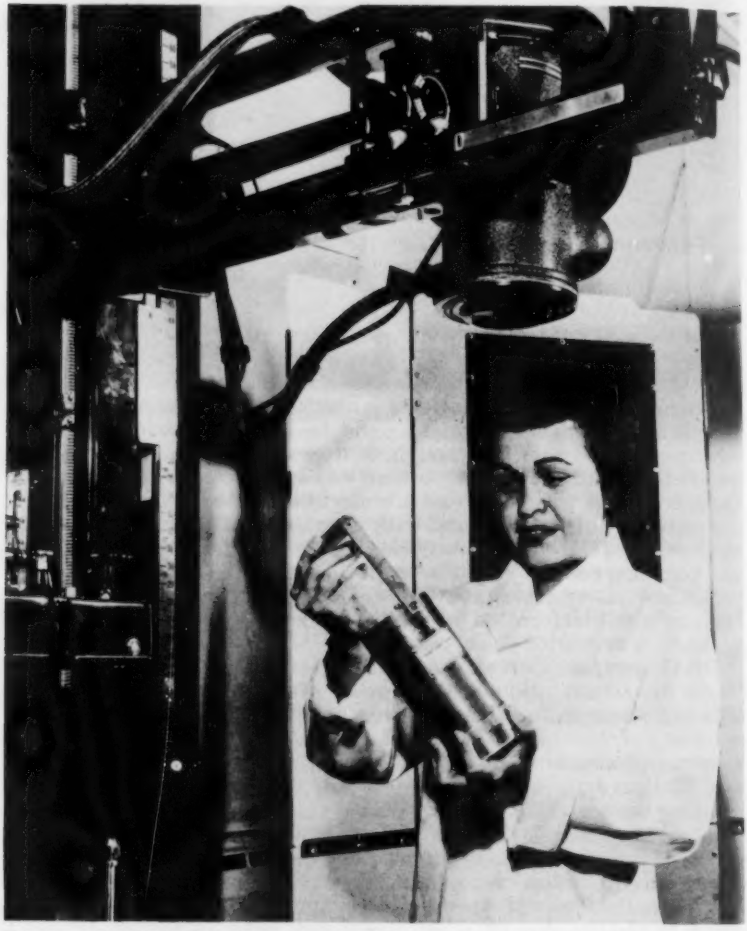

EXHIBIT 49.—Radio thulium diagnostic X-ray unit designed by the Argonne National Laboratory.

In this lead shield container is a source of thulium 170, and it is arranged with a small motor inside to drive the shutter. Here I have a little portable battery set to drive the motor. I am unscrewing from the top an extra lead safety shield, which gives added protection, so that this whole unit can be carried around, and the technician receive less than the permissible daily level of radiation.

Representative HINSHAW. That is a very portable X-ray machine, then?

Dr. HASTERLIK. Yes; the whole unit weighs less than 10 pounds.

Representative HINSHAW. As against how many hundreds of pounds for the ordinary X-ray machine?

Dr. HASTERLIK. The average Army field portable unit, although it is called portable, has to be transported on a jeep. You can see that this is radioactive, because the counter here is ticking. I am not going to open the shield, because there is no reason for any of us to be getting extra radiation. But with this unit and a long cord one can do radiography by merely pressing this button and opening this shutter. This brings the source into an exposed position.

I don't believe that such a unit will ever replace conventional radiography in a hospital.

Representative HINSHAW. Is that for therapy, or just X-ray pictures?

Dr. HASTERLIK. This is just for X-ray pictures. This probably won't be used in hospitals for usual diagnostic radiography, because in conventional radiography one chooses different energy X-rays, depending on the part that one wants to X-ray. When one radiographs dense bone one uses higher energies, or with soft tissues lesser energetic X-rays, and with this unit we are confined to certain energies and no others.

But for Army-Navy field use, for civilian defense, for casualty units in a city, this unit makes it possible to do radiography on the spot.

Representative HINSHAW. Is it for location of bullets, and that sort of thing?

Dr. HASTERLIK. Yes; one could use this very easily for the location of foreign bodies.

Representative HINSHAW. And one could get a photograph of that at right angles very easily by just moving it around.

Dr. HASTERLIK. Yes, sir. I don't believe we will ever be able to do flouroscopy with this unit, because the dose rate, even with the most active source that it would be possible to make from the physical considerations, would not yield a high enough dose rate. I think fluoroscopy is out. But one can rig up a field unit, I think, using equipment, such as the Picker-Polaroid unit with a film pack. With such a unit one can do radiography on the spot and develop the film on the spot. I have done this already. The developing unit could be modified so as not to need any electrical connections, either.

Representative HINSHAW. In what sorts of cases have you used it on the spot? In what sort of case is it applicable?

Dr. HASTERLIK. Since we do not like to give ourselves or our friends any more radiation than necessary, I have been using standard phantoms, which are bones imbedded in a wax, the same density as tissue. For experimental studies this is just as good as using people.

Representative HINSHAW. What industrial uses would it have, do you think?

Dr. HASTERLIK. This would be very useful in industry for radiographing light metals, and for determining the heights of columns of liquids or metals in closed systems. One could use this as part of an automatic signal for servomechanisms. There could be very many industrial uses for it.

Representative HINSHAW. Is thulium an expensive material?

Dr. HASTERLIK. Thulium is one of the rare earths. The rare earths are actually common in the earth's crust. They are only called the

rare earths because until recently they were difficult to separate one from the other. But Dr. Frank Spedding at the Institute for Atomic Research at Ames, Iowa, has been able to develop a method for the production of thulium which would make it very reasonable. In fact, it would seem that the cost of the metal for a source such as this would be somewhere in the range of between $50 and $100, which is certainly very reasonable.

Representative HINSHAW. What do you anticipate such a piece of equipment could be manufactured for in quantities of a thousand, or thereabouts? Any other number close to it would be all right.

Dr. HASTERLIK. I would think these units could be made, not counting the cost of the radiation service and of the neutrons—I know nothing about those costs—just for the thulium and the shield, not more than $200 to make such units. What the irradiation costs would be, I do not know.

Representative HINSHAW. I am not suggesting that any one go into the business, but it sounds like a very promising undertaking.

Dr. HASTERLIK. There is one limiting factor, though. The half life is only 129 days. For this to be a useful device, one must make arrangements to receive a new source at regular intervals. I think the source is perfectly usable for 9 months to a year.

Representative HINSHAW. Then it must receive very concentrated use during that period of time to make it a profitable venture. But in industry it would have such a constant use, no doubt, for some purposes that industry might devise.

That is a very interesting device. Is Argonne National Laboratory responsible for it?

Dr. HASTERLIK. The Argonne National Laboratory designed the shield and source and did the work on the physics of the units, and the Argonne National Laboratory at our suggestion made available to us and to the Army sources for studies on the medical applications and radiography. So the Argonne National Laboratory is essentially responsible, one for the development of the physical end of it, and our hospital for the development of the medical aspects.

Representative HINSHAW. We thank you very much, Dr. Hasterlik. It has been a very interesting discussion, very profitable, and I know those who read the record after us will be tremendously enlightened on subjects which they had not even imagined.

Dr. HASTERLIK. Thank you very much. It was an honor and a pleasure to appear before this committee.

STATEMENT OF DR. E. M. K. GEILING, PROFESSOR OF PHARMACOLOGY AND CHAIRMAN OF THE DEPARTMENT AT THE UNIVERSITY OF CHICAGO

Representative HINSHAW. We shall now be indebted to Dr. E. M. K. Geiling, Frank P. Hixon, distinguished service professor of pharmocology at the University of Chicago and chairman of the department, for a discussion of the biological method of preparing radioactivity labeled drugs of medicinal importance. He will also demonstrate the transference of radioactivity from a plant to garden slugs feeding on the radioactive plant; and the subsequent transfer of the radioactivity to a toad through feeding on radioactive slugs.

Dr. Geiling was born in the Orange Free State of South Africa. He received his bachelor of arts degree at the University of South Africa, his master of science and doctor of philosophy degrees from the University of Illinois. After studying at the University of Capetown and Yale University, he went to Johns Hopkins and received his doctorate of medicine in 1923. He has been president of the American Society of Pharmacology and Experimental Therapeutics, as well as president of the Society for Experimental Biology and Medicine. He has published many articles in the field of pharmacology, notably work relating to the pituitary gland in, of all things, the whale. This work took him on many field trips on the high seas.

When radioisotopes became readily available, he was one of the first to attempt to exploit these new tools in the advancement of his chosen field of science.

Dr. Geiling, you have chosen to leave a perfectly beautiful section of the world, South Africa, and Capetown, which I have visited, and come to America. And as for doing work in connection with the pituitary gland of the whale, I cannot conceive of anything more exciting than hunting of a whale to work on his pituitary.

We will be very interested in the presentation that you have to make on the biological methods of radioactively labeling drugs for various purposes.

Dr. GEILING. Mr. Chairman and members of the Joint Committee on Atomic Energy, on behalf of my colleagues, I want to express our appreciation to you for the opportunity of telling you briefly about some of the highlights of the project which we have chosen to label The Preparation of Radioactive Drugs of Medicinal Importance by the Process of Biosynthesis.

The word "biosynthesis" means the process of using living plant or animal tissue for the purpose of producing a specific compound which cannot be conveniently prepared by the chemist in his laboratory. In this procedure nature does for us a job which as yet the chemist has been unable to do.

The drugs that we have selected to work on first are of great medicinal importance and have been known for a long time. They have complex chemical structures; they are extremely useful in serious diseases and are used in very small quantities. There have been many advances made regarding their use in clinical medicine but we know very little or nothing about the way they are used in the body, their path of excretion, and most important of all, their breakdown products.

When certain of the radioisotopes became available for unrestricted study, there was placed in the hands, not only of pharmacologists, but also of all scientists working in the biomedical fields, a new and extremely sensitive method for tracing the minutest quantity of a drug or food product throughout the body. The extreme delicacy of these new techniques enables one now to carry out experiments which hitherto were not possible, because the biological and chemical methods available were not sensitive enough. Even if these methods were sensitive enough, they are not sufficiently specific to detect the breakdown products. Another unique feature of the radioactive isotope technique is that one can follow the course of the unchanged drug in all the organs and tissues as well as the excretory products. By the simple technique of isotope dilution one can remove the unchanged

drug, and the remaining radioactivity will represent the metabolite or the breakdown products of these medicinal substances. I may add that particularly in this day and age, when there are so many new substances being brought into medicine, the basic fact remains that the physician and the experimentalist want to know: How the body uses the drug, where the drug accumulates, and what is the breakdown product? With the use of this new technique, we have available a means of extending the horizon or widening the frontiers of knowledge.

One further advantage of this new technique is that it brings together workers in different fields. In our research work which will be presented today, we have enlisted the aid of botanists, zoologists, chemists and, of course, individuals skilled in radioactive isotope techniques. We have also had the opportunity of using the Argonne Cancer Research Hospital to test some of these drugs on patients which have been selected for special study. Another important point: we have been able to arrange our program of studies in such a way that in the past 6 or 7 years we have trained, with the aid of funds from the Atomic Energy Commission, about 17 people for work in the field of pharmacology, with special reference to the use of isotopes. So you can see that collectively we have the opportunities of broadening our knowledge and bringing together the knowledge of different disciplines and that is one of the best ways to extend our knowledge in this and allied subjects. And while we don't have a great deal in the way of actual practical application of our work, you can see the potentialities are very far-reaching.

Let me now briefly tell you about a few of our significant findings.

You will notice that in these charts (exhibits 50, below, 51, p. 105) we have set down a brief summary of our work. The technique is simple. We have available actively growing medicinal plants, samples of which are before you. They are placed in sealed chambers with adequate illumination, with openings for the introduction of nutrients and also for the introduction of radioactive carbon. Then they are allowed to grow for a period of 2 months or so, depending upon the nature of the plant. At the end of that period, the plant is harvested, and the drugs are extracted by the appropriate technique.

Representative HINSHAW. You are speaking of radioactive carbon, as carbon 14?

PREPARATION of RADIOACTIVE DRUGS by BIOSYNTHESIS

Actively growing medicinal plants are enclosed in air tight chambers with openings for injection of radioactive carbon dioxide and nutrient solutions. With proper light and temperature, plants grow in these chambers for several months. During their growth period radioactive carbon dioxide is assimilated by the plants which synthesize radioactive drugs.

RADIOACTIVE	MORPHINE	from	POPPY
"	DIGITOXIN	"	DIGITALIS PURPUREA
"	NICOTINE	"	TOBACCO
"	ATROPINE	"	BELLADONNA
"	COLCHICINE	"	COLCHICUM AUTUMNALE
"	VERATRUM ALKALOIDS.	"	VERATRUM VIRIDEI

EXHIBIT 50

EXHIBIT 51

Dr. GEILING. That is right, sir. All of our work was done with radioactive carbon. The advantages of radioactive carbon are, first of all, that it has a very long half life, and perhaps equally important is the fact that natural carbon is present in all plant and animal tissues. C14 is available in the form of barium carbonate and the radioactive carbon can be liberated in the form of carbon dioxide which can be easily introduced into the chamber; the plants take it up and incorporate it into all their constituents; and a similar thing would happen in the case of animals. Therefore, it is a unique ma-

terial to work with. And furthermore, it has only the beta radiation, which can be easily shielded against, and which can be readily counted. So we may say in ordinary parlance that it is a tailormade material for work of this kind.

The labeled drugs which we have chosen to discuss briefly today, Mr. Chairman, are morphine, which comes from the poppy plant, and digitoxin, which comes from the digitalis purpurea, nicotine from tobacco, atropine, colchicine, and the veratrum alkaloids.

There are other drugs which we have made radioactive. You may be interested to know that we have made the ordinary ragweed radioactive. The ragweed is grown from seed, the plants are exposed as we will show you in a minute, and the pollen and the rest of the plant is made radioactive; so that the allergist may be able to see the difference between the sensitive and the nonsensitive patient. And I can give you many other instances in which this technique can be made available.

Then, as I will show you in a few minutes, one can turn good into evil. In growing these plants one always has to combat their natural enemies, and one of these is the ordinary garden slug. One may feel all elated when one sees that the plants are growing beautifully, but the next morning one finds just a few stubs left. The little slug has done his dirty work and then goes into hiding. So we decided we would turn good into evil. Since the slug does not know the difference between the radioactive plant and the normal plant, we made a plant radioactive and told Mr. Slug to go ahead and enjoy himself, and he did so. As a result he was made very radioactive. And in turn we decided to see if the transference of radioactivity could be accomplished. We took the slug, and pushed it down the throat of a toad which is a sluggist creature. In a short while we applied the geiger counter to the toad and found that the toad also became radioactive.

We had a special purpose in selecting the toad which has a great deal of historical and also medical interest (exhibits 52, 53, and 54, pp. 107 and 108). The use of the toad as a medical product goes back to great antiquity. The ancient Chinese had by empiricism discovered that the toad has a secretion in the skin which, if given to a patient with dropsy, which we now know as heart disease, would relieve the patient.

Representative HINSHAW. Was it Macbeth in Shakespeare's play who dealt with a witch that brewed some concoction of toads, and so forth, snake's venom, and a lot of other things?

EXHIBIT 52.—Dr. Geiling demonstrating the secretion by toad of bufagin containing a digitalislike material.

EXHIBIT 53.—Radioactive slugs in left foreground; radioactive plants in background; bufa agua in right foreground.

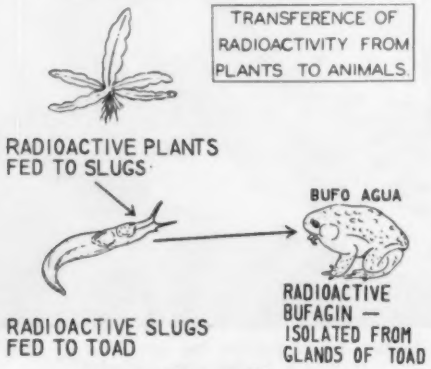
TRANSFERENCE OF RADIOACTIVITY FROM PLANTS TO ANIMALS.
RADIOACTIVE PLANTS FED TO SLUGS
BUFO AGUA
RADIOACTIVE SLUGS FED TO TOAD
RADIOACTIVE BUFAGIN — ISOLATED FROM GLANDS OF TOAD

EXHIBIT 54

Dr. GEILING. Mithridates tried to use it, too, when he wanted to shield himself against all evil. Mythology is replete with the use of toads.

Representative HINSHAW. But have you made these doctors of medicine believe that toads are medicinal articles?

Dr. GEILING. You can only lead a horse to the water. You can't make him drink, sir. We do the best we can. I think they have been very receptive to it. It is well known in medicine that the secretion from the toad has an activity very similar to that which one obtains from the plant digitalis. But in addition to the substance called bufagin, there is also adrenalin.

Now, may I also say that toads were used by the ancients when they had to hunt for their food with bow and arrow. They covered the tips of their arrows with this secretion, arrow poison, which we will see in a minute. And that was very useful to them. Because when they wounded the animal, then the animal began to bleed and if the heart got the stimulation through the digitalis and epinephrine, he lost his blood more rapidly than he would otherwise, so that the hunter was sure of his prey. I could tell you many other stories, but I think I had better go on with my assigned topic.

You can see in a very general way what we are trying to do. I now just very briefly show a growing chamber drawn in outline form (exhibits 55, 56, and 57, pp. 110, 111, and 112.) These chambers are at the University of Chicago, and here again we are in close cooperation with your group out at the Argonne National Laboratory.

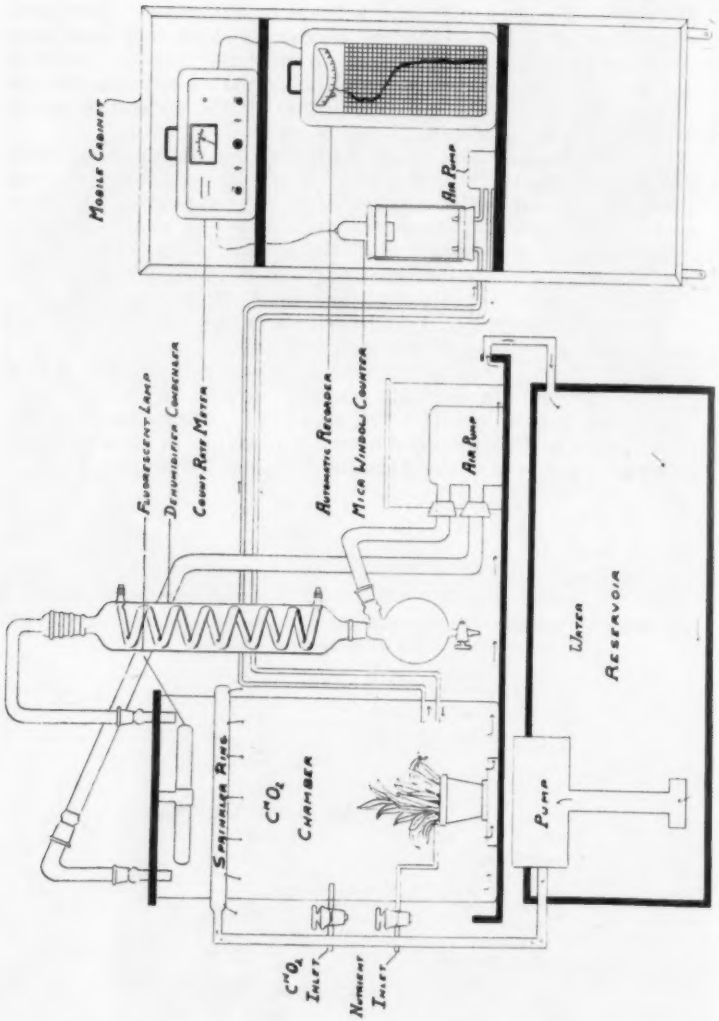

EXHIBIT 55.—Chamber, for exposing growing plants to radiation, at the University of Chicago.

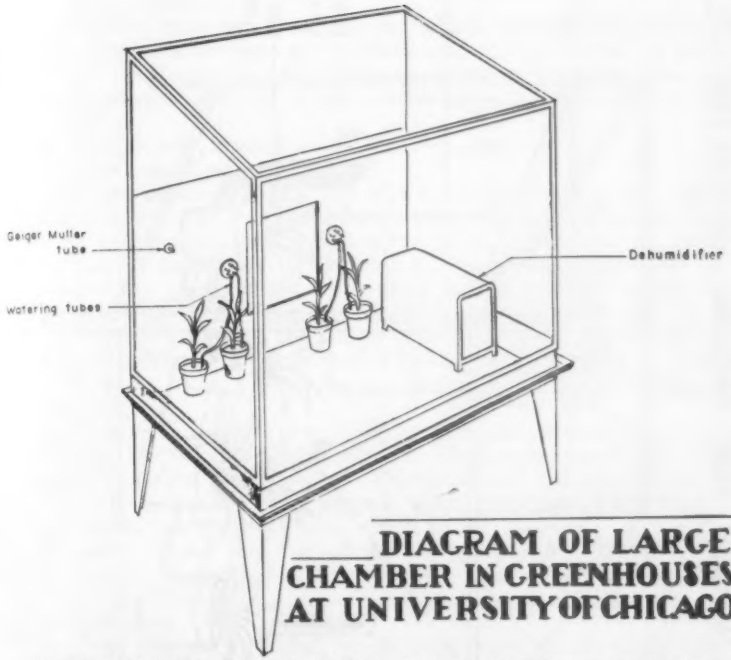

DIAGRAM OF LARGE CHAMBER IN GREENHOUSES AT UNIVERSITY OF CHICAGO

THIRTY PLANTS CAN BE GROWN IN CHAMBER WHICH IS EQUIPPED WITH DEVICES FOR CONTROL OF TEMPERATURE AND HUMIDITY. SIZE OF CHAMBER: LENGTH 7'-7", WIDTH 3'-6", HEIGTH 6'-6"

EXHIBIT 56

Exhibit 56.—Chamber, for exposing growing plants to radiation, at the University of Chicago.

PLANT CHAMBER FOR GROWING RADIOACTIVE PLANTS

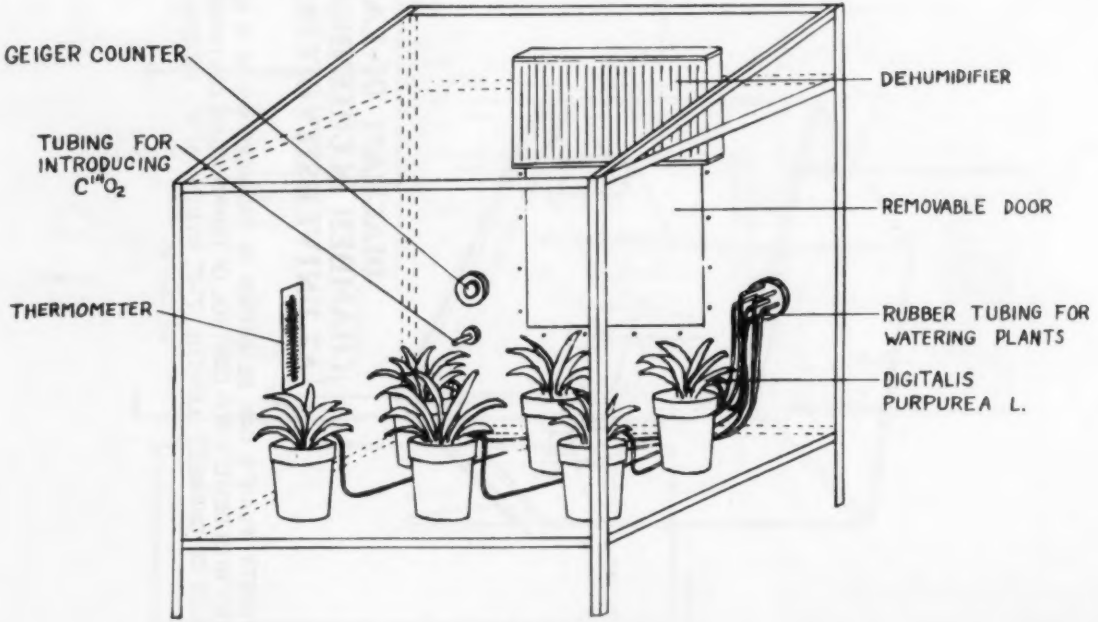

EXHIBIT 57

This chamber represents in simple outline an airtight glass case supplied with a Geiger counter and tubes for introducing radioactivity. And these represent actively growing plants. Each plant is supplied with a watering tube, through which we can give water and nutrient solutions. These happen to be digitalis. Inside the chamber we have a thermometer and a dehumidifier. And then, of course, we have a light source. So that actually we know now, and others have known it too, that when you have the proper illumination and the humidity controlled and also the temperature, the plants will grow perfectly normally, those that flower will grow to flowering, and seed will be formed.

Here again I may say that the seed which we obtained from the radioactive plants are used by our botanists and geneticists to study the effect of radiation at different dosage levels on the successive generations, and also what effect radioactive materials will have on the chromosomes.

This, then, briefly, is what we do with chamber.

Now, may I show you the next?

Among the plants, I would just like to emphasize that each plant has a little story of its own; here we have a growing poppy plant from which we obtain morphine, which is the drug of choice in the treatment of severe pain. But it also has a tremendous sociological importance at the present time. The dope evil is one with which the medical profession must concern itself. And we believe that if we find out the mechanism of the action of morphine, we may be able to throw some light on the fundamental biological mechanism of addiction. This is a hope. We promise nothing. We can only express the hope, sir.

Here we have the mature poppy plant. The main source of the drug comes from the capsule which you see illustrated over here. The flower forms. First of all, the petals drop off and the capsule is then left. And it is the immature capsule which we harvest, and that is what gives the latex, if you will, which in the form of a ball, is the crude opium. From that we extract the morphine which is radioactive. And with that radioactive material, we can pursue the studies which we have planned. And each drug, of course, is used for a specific set of studies.

May I tell you very briefly, by omitting some of the procedures about the next drug?

It is colchicine, in which, I believe, you will be especially interested. Colchicine, too, has a long medical history. There are many rhymes about colchicine being used in gout. Actually we have found many facts regarding the use of colchicine. The one fact I would like to illustrate is the distribution of colchicine in a normal mouse, and in the same strain of mouse, into which an experimental tumor has been injected.

Now, may I call your attention to this chart (exhibit 58, p. 114). This is a distribution of the radioactive colchicine in organs of three different strains of mice.

May I focus your attention on the spleen particularly? You will notice that there is a considerable amount of radioactive colchicine in the spleen of these three different types of normal mice. There

is no colchicine in the heart, or the brain, or the muscle. There is some in the intestine, some in the kidney, and some in the liver. If you take animals from the same three strains of mice and inject into them an experimental tumor and allow it to grow, maybe to the size of a large pea or bean, and then inject into those mice labeled colchicine, you will find a very different pattern of distribution. (Exhibits 59 below and 60, p. 115.) Now, you will find in those tumor mice that the spleen which in the normal mouse has a good deal of colchicine has no colchicine whatsoever. And this experiment has been repeated a good number of times on different strains of experimental animals.

DISTRIBUTION OF RADIOACTIVE COLCHICINE IN ORGANS OF 3 DIFFERENT STRAINS OF NORMAL MICE

	Per Cent						
	Intestine	Kidney	Liver	Spleen	Heart	Brain	Muscle
C-57 (black)	22.8	29.6	9.4	39.2	0	0	0
Hybrid A	19.2	22.6	15.1	43.1	0	0	0
White Swiss	18.3	26.2	7.4	47.1	0	0	0

Data give the counts found in each organ as percentage of the total recovered. Each value represents an average of at least 10 animals.

EXHIBIT 58

DISTRIBUTION OF RADIOACTIVE COLCHICINE IN ORGANS OF TUMOR-BEARING MICE

	Per Cent				
	Intestine	Kidney	Liver	Spleen	Tumor
C-57 Sarcoma-180	45.3	29	7.5	0	18.2
Hybrid A Spindlecell Sarcoma	39.5	28.1	19.0	0	13.4
dba x C3H Mammary carcinoma	38.2	30.7	18.5	0	12.3
White Swiss mice Ehrlich Ascites carcinoma	39.8	26.7	26.7	0	6.8

Data give the counts found in each organ as percentage of the total recovered. Each value represents an average of at least 8 animals.

EXHIBIT 59

TISSUE DISTRIBUTION
OF RADIOACTIVE COLCHICINE IN NORMAL
AND TUMOR BEARING MICE

	NORMAL	TUMOR
KIDNEY	29.5	29
LIVER	9.8	7.5
INTESTINE	22.3	45.3
SPLEEN	38.4	0
TUMOR	—	18.2

DATA EXPRESSED IN % OF DRUG ACCUMULATED

TUMORS STUDIED:
1. SARCOMA 180
2. SPINDLE CELL SARCOMA
3. MAMMARY CARCINOMA
4. EHRLICH ASCITES CARCINOMA

EXHIBIT 60

We interpret this to mean that there is something in the tumor which inhibits the spleen from taking up the colchicine.

We have extended our studies considerably further. One can let a mouse develop a tumor, and after the tumor has grown, one may remove the tumor and let the mouse recover. After some time, that mouse which had developed the tumor will behave like a normal mouse. If one takes that tumor which one has removed, grind it up, and inject it into normal mice, and wait for a period of 24 or 48 hours—the longer you wait, the more pronounced your experiment is—and after that the animal into which you have injected that experimental tumor now behaves exactly like a mouse which has had a tumor growing in it. In other words, the material from the tumor has been given off and has been circulated in that animal's body so that it acts as an inhibitor to the uptake of colchicine by the spleen.

The significance of this important fact we are trying to determine. We have made extracts of the tumor and have purified the particular principle which is active in the inhibition of the uptake of colchicine by the spleen.

I believe it would be a little too early to give you any specific information other than to say that we have the feeling, at present, that the pattern of distribution of this drug is different in the cancer patient than it is in the normal patient.

I want to take the opportunity, with your permission, Mr. Chairman, to emphasize that this is not a test for cancer. It is just too dangerous to make any such inference. The drug is still an experimental tool; its value we are trying to ascertain.

Now, may I take just a few more minutes to tell you about the digitoxin?

DAILY RENAL EXCRETION RATES OF RADIOACTIVE DIGITOXIN AND ITS METABOLIC PRODUCTS IN CARDIAC PATIENTS

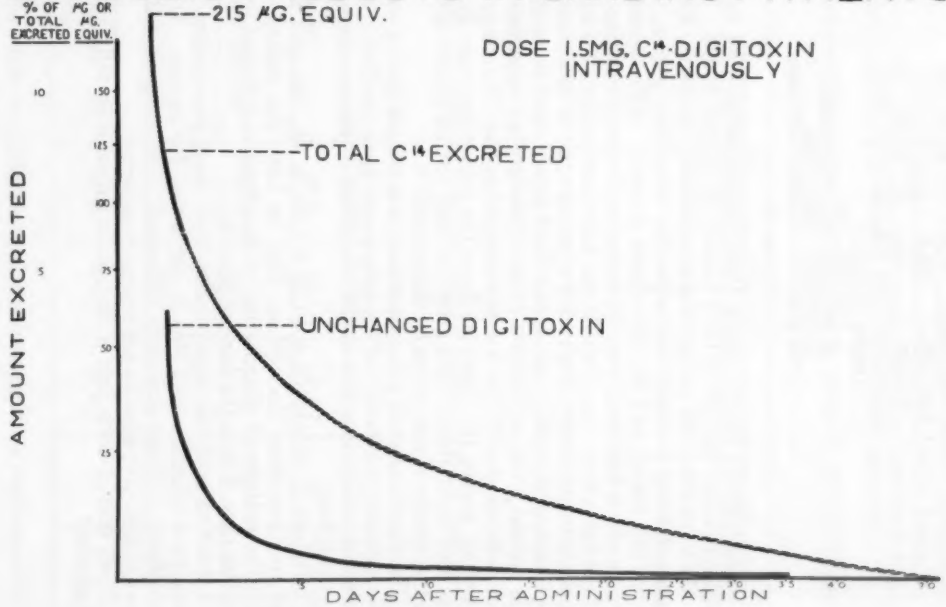

EXHIBIT 61

This chart (exhibit 61, p. 116), I say it with all modesty, Mr. Chairman, presents the first experiment where one has been able to inject a very small dose of the active principle from the digitalis plant, which has been used millions of times on patients suffering from all types of heart disease, and follow it through the body. By the use of this technique, we are able to follow the course of a single therapeutic dose, which you see registered on the chart, in a patient that has been standardized and who agreed to undergo this experiment. One can follow the excretion of 1 milligram of this drug over a period of 35 days. The point of special importance is that, even after the unchanged drug is no longer present in the urine, for a number of days afterward the metabolic or the breakdown products of the original drug can still be ascertained in the urine; which is again, I believe, one of the most significant ways of demonstrating the extreme, I may say unbelievable, delicacy of this new technique. And the significance here, I might indicate, is that it now gives us a chance to collect the split products and see first of all whether they have any activity like the parent drug and then afterward see what is the nature of them.

Now with the few remaining minutes may I demonstrate some of these things?

This, then, is the story of the transfer of radioactivity from plant to animal, and from one animal to another.

We have to shield these specimens because we don't want to distribute radioactivity unnecessarily. This happens to be the lettuce. The slugs for this purpose are made radioactive by feeding them the lettuce, which takes up radioactivity very easily. And I have covered it very carefully, but will hold this open end to the Geiger counter. This is merely to demonstrate that this plant has radioactivity. And the plant, if you don't overdose it with radioactivity, will grow perfectly normally.

If one feeds, as we have done in this case, these slugs, which I can demonstrate to you over here, with radioactive lettuce, you will see that they have become radioactive. Would you mind just applying the Geiger counter here? [Counter records marked radioactivity.]

Now, if one takes that radioactive slug and puts it down the throat of this large toad—one may use half a dozen or more of the slugs—and then leaves the toad in a sealed chamber with the proper exchange of air, the toad will become radioactive.

(Dr. Geiling removed the toad from the box, first covering his hand with a cloth.)

I have to do that, Mr. Chairman. Toads are a little careless in their habits.

The main point of interest is this large gland on the neck of the toad. There you will see a lot of little fine holes or crevices. Now, if this toad is irritated, then he begins to exude this secretion. And I will attempt to do it and show you. This is the secretion which contains the digitalislike principle, and also adrenalin. When this toad is fed radioactive slugs, all this material becomes radioactive. And that is one of the programs which was completed under the study which I am now presenting to you. Other uses can be made of it, because the slug is easily digested, and it has a great deal of nutrient. The toad has a slow metabolism, slow turnover, so that all parts of the toad become very readily radioactive.

EXHIBIT 61

We secure these toads from Bermuda. Each different species has a slightly different content of the active principles.

You may be interested to see some of these other plants which are actually growing. [Specimens of other medicinal plants were shown.]

This is an actual poppy plant, from which you get the morphine. If you look closely, Mr. Chairman, you will see that that bud is just beginning to form. And this is the mature capsule. If you cut this capsule and squeeze it, you will get a white secretion, which hardens, and that is called the latex from which the morphine is extracted. The poppy plant has certain cultural pecularities and it is handled in the greenhouse. A study of its cultural characteristics has been the subject of an extremely interesting thesis from the department of botany. The graduate student worked out the optimum conditions for the yield of the maximum amount of morphine. This poppy plant, under certain conditions, can grow high and have no morphine. And yet if you give it a long daylight, you can get a small plant to give a great deal of morphine.

The digitalis plant is right here. This is one that is actually in bloom. In practice, it is from the dry leaf that one gets the digitoxin. But if you allow this plant to grow to maturity in a chamber in the presence of radiocarbon, all parts of the plant become radioactive. These seed pods which are forming here will also be radioactive. An actual experiment is now in progress with plants in the second generation which are grown from radioactive seed. That is, of course, a study in which we are only cooperating. It is the botanist and the plant physiologist that are doing the work

Mr. Chairman, I think I have taken enough of your time.

I appreciate the opportunity of telling you about our work. We want to emphasize that this new and delicate technique opens many vistas to the pharmacologists and other scientists as well. We should certainly, in a short time, know a great deal more about the way the drugs behave. And the moment we know that, I think we can open up the way for the development of better and more useful drugs.

Thank you, Mr. Chairman. I have prepared a summary of my discussion, a copy of which you have before you.

(The summary referred to follows.)

Biosynthesis of Radioactive Drugs of Medicinal Importance

Synopsis of discussion presented before the Joint Congressional Committee of the Atomic Energy Commission in Washington, D. C., on June 3, 1954, by E. M. K. Geiling, M. D.; Frank P. Hixon, distinguished service professor of pharmacology, University of Chicago School of Medicine, Chicago, Ill.

SUMMARY

The radioactive isotope technique has enabled the pharmacologist to study many problems which previously could not be undertaken because the available biological and chemical methods lacked the desired sensitivity. Many of our valuable drugs (1) have complex chemical structures, (2) cannot as yet be prepared synthetically, and (3) are administered to patients in such small doses that, when distributed in the tissues, they cannot be detected by the presently available biological or chemical methods. Some of the available methods may be able to detect the unchanged drug, but not its metabolites. However, the isotope technique, because of its extreme sensitivity, permits the detection not only of very minute amounts of the drug, but also its metabolic products.

All of our labeling of drugs was done with carbon 14 (C^{14}) which has the following advantages:

(1) It is present in all organic compounds.

(2) In the form of $C^{14}O_2$ it can easily be incorporated into growing plants.
(3) It has a long half life which makes long-time experiments possible.
(4) It has only soft beta radiations which are easily shielded against, but can be readily measured.

BIOSYNTHESIS

Radiocarbon is incorporated into living plants by the process of biosynthesis: i. e., allowing a plant to form the desired compound by supplying the tagged element in a form which the plant can assimilate. Plants are grown in a $C^{14}O_2$ chamber equipped with an adequate light source and a dehumidifier. After several weeks, the plants are harvested, the drugs are extracted and then purified by appropriate procedure.

To date, the following drugs have been biosynthesized: digitoxin, morphine, nicotine, atropine, colchicine, podophyllotoxin, the veratrum alkaloids, and ragweed pollen.

Purity of the labeled drugs was determined by physical and chemical methods. Experiments were performed on different species of animals in order to establish that the biological activity of the labeled drugs was identical with that of the nonradioactive compounds.

EXPERIMENTS WITH RADIOACTIVE DIGITOXIN

Therapeutic doses of labeled digitoxin have been given to selected patients with heart disease in the Billings Hospital at the University of Chicago.

To date excretion and blood level studies have been completed on eight patients. We find that the drug and its metabolites do not disappear rapidly from the blood stream, but are present in the vascular system for days. Excretion is mainly in the urine and continues for many days. Eight percent of the unchanged drug appears in the urine and about the same amount in the feces. About 75 percent of the drug, in the form of metabolites is excreted in the urine.

Tissues from three cardiac patients who were given small doses of the labeled drug some hours before exodus have been studied. We find that the drug in these patients did not accumulate in the heart, but seems to be mainly metabolized in the liver and then enters the enterohepatic cycle with ultimate excretion chiefly as metabolites in the urine. The concentration of the drug on a tissue weight basis is higher in the liver, the gastrointestinal tract, gall bladder and kidney, than in the heart, skeletal muscle, and lung. Studies are now in progress to determine the effect of repeated doses.

Future plans include a study of patients with bile fistulas and a study of the placental transfer of the drug in suitable patients.

STUDIES WITH LABELED COLCHICINE

The distribution of radioactive colchincine has been determined in normal and in tumor bearing mice. It was found that normal mice have a large concentration of the drug in the spleen while the tumor bearing mice show no colchicine in this organ. The tumor mice have twice as much colchicine in the intestine as do the normal mice.

The excretion pattern of radiocolchicine in normal mice differs from that found in tumor mice. Normal mice excrete six times more unchanged colchicine than the tumor-bearing mice. The excretion of radioactive colchicine in patients in the Argonne Cancer Research Hospital with and without neoplastic disease is now under investigation. We found that a similar difference in the pattern of excretion holds for human patients as was observed in normal and in tumor mice.

We are also studying the mechanism by which tumor mice have an altered metabolism of colchicine. This distribution pattern of the drug in tumor mice can be duplicated in normal mice if they are pretreated with tumor extracts.

STUDIES WITH LABELED MORPHINE

High activity radiomorphine has been prepared in this laboratory and is being used in distribution studies in normal and addicted animals. Mechanisms of morphine antagonism using C^{14} glucose and several compounds related structuraly to morphine are also being investigated. As the depressant action of morphine appears to be intimately linked to carbohydrate metabolism, an attempt will be made to identify the intermediates accumulating in the brains of morphinized animals.

Similar studies on experimental animals are now being conducted with labeled atropine, podophyllotoxin, α peltatin, and β peltatin. Experiments with purified labeled ragweed antigen are being carried out in the Allergy Clinic of the Billings Hospital.

Tropical toads have been made radioactive by feeding them radioactive garden slugs or algae which were grown in a media rich in carbon-14. Radioactive bufagin, a digitalislike glycoside and epinephrine were obtained from the parotid glands of the radioactive toads. The distribution of carbon-14 in toad tissue was measured and compared with the distribution of carbon-14 in rats under similar conditions. Bufagin was also used for enzyme studies in which the action of this drug on the enzymatic reactions of the mammalian heart was measured.

Representative HINSHAW. That was a most interesting discussion, Dr. Geiling.

Dr. GEILING. Thank you, sir.

Representative HINSHAW. I should like to hear more, and we will hope to, at another time, visit you in your laboratory.

Dr. GEILING. Thank you, sir.

Representative HINSHAW. At the time perhaps you will tell us somethings about the pituitary of the whale.

Dr. GEILING. I will be glad to demonstrate it to you, sir. If I had known of your interest, I could have brought one along.

Representative HINSHAW. A whale, or a pituitary?

Dr. GEILING. I could bring you a picture of one of the whales, but I could bring you the pituitary gland itself, which is about 3 inches long, 1½ inches wide, and about one-half inch in thickness. The size of the whale is no index of the size of the gland. In fact, it is in inverse proportion. While the pituitary gland of the whale is very large when compared to the gland of other animal species, it is very small in proportion to the total weight of this gigantic animal.

Thank you, sir.

Representative HINSHAW. That has been a most interesting discussion. And I would like to say to the people of South Africa that they have lost a very valuable citizen and we have gained one. I take it that they have gained enough from us in our citizens who have gone there to live, to in part make up for that loss.

STATEMENT OF DR. JOHN C. BUGHER, DIRECTOR, DIVISION OF BIOLOGY AND MEDICINE, ATOMIC ENERGY COMMISSION—Resumed

Representative HINSHAW. The next witness will be our old friend, Dr. John C. Bugher, who is the Director of the Division of Biology and Medicine of the Atomic Energy Commission. We all know him very well. He has been introduced as the head of this program. And he will tell you something of his studies in the spread of disease among animals, using radioactively labeled insects, and give a demonstration of the use of radioactive mosquitoes. This was the work in which Dr. Bugher, I understand, was engaged before he came to the Atomic Energy Commission.

Is that correct, Doctor?

Dr. BUGHER. That was one phase of it.

Representative HINSHAW. Well, we shall be most interested in hearing about that subject specifically from you who are so well versed in it.

Dr. BUGHER. Thank you, sir. I have changed my function, you see, in this hearing, and I take part in the technical discussion as well.

The point of the discussion which I wish to present to you is the general problem of the utilization of nuclear techniques in epidemiology—the mechanics of contagion.

This is in itself an enormous subject, and I think it is one that is pertinent to all discussions of public health, because our attack on diseases that affect populations has to be based upon an accurate knowledge of the mechanisms by which the infection is spread from individual to individual.

We have, in general in this whole complicated system of cycles and varying mechanisms, three essential components: one is the mammalian component, which may be man, or a domestic animal, or a wild animal, which may fall victim to the infectious agent; and second, the infectious agent itself, which may be a micro-organism, a filterable virus, or any one of a great variety of living things; and then third, the transmitting agent, or the vector, which very commonly is to be found among the arthropods, that is, the general category of living things, of which the insects are a part.

Now, the problem of control is essentially that of determining precisely and quantitatively every step in this complicated cycle, so that one may look for the weak spot in the cycle. The public health official then directs his attack to that weak spot, with the expectation of breaking the cycle, and thus preventing the further propagation of the infectious agent to other individuals.

The whole subject is one of almost infinite complexity. It may vary from a simple epidemiological mechanism such as in influenza, where a virus is spread directly from one individual to another by way of the respiratory tract, to a more elaborate scheme in which an insect may pick up the infectious agent from one individual, carry it in its own body, perhaps requiring a certain time for the evolution of the parasite within the insect's body, and then in turn transmitting it by bite or otherwise to an uninfected individual. A good example of the latter is malaria, wherein the malarial parasite taken up from the bloodstream of the man undergoes further modification in the body of the anopheles mosquito, the means by which it is carried from man to man. After a sufficient period in which the parasite undergoes its changes, the mosquito can transmit the infection by bite releasing parasites from its own salivary glands through its proboscis into the subcutaneous tissue of the individual.

As an example, I will discuss a system which is still more complex in that many species of animals, among which man may be included, may be involved, and several species of mosquitoes may participate.

In order for a mosquito to become infected from an animal or a human being having a particular disease, it is necessary that the individual carry the infectious agent in such a manner as to permit the insect to have access to it. In the case of the mosquito, it means that the virus must be circulating in the bloodstream of the man. The mosquito, on biting him, removes a small amount of blood and itself becomes infected with the virus. After an appreciable period of time, it becomes capable of transmitting. There is an incubation period in the mosquito itself.

In order for the mosquito to become infected, it must, of course, reach the man. It means that the environmental conditions must be such as to favor the access to the individual by the mosquito.

Then, in turn, after the period of incubation, in order for the mosquito to be capable of transmitting, it has to have access to another individual under suitable conditions.

This has meant that our great problems of infectious disease transmitted by insects in general lie in the Tropics, where cycle after cycle may continue without the blocking due to frosts and death of insects due to such climatic things. So climate becomes an important factor here, in the whole problem of ecology.

Other factors are those that have to do with the biological balance and behavior of the insect itself. The length of life of the insect is an important factor. If the insect is unable to survive longer than the incubation period of the virus, it cannot function as an effective vector of the particular disease.

In this whole mechanism, the animal and the mosquito not only must be in the same general environment, but they must in fact occupy the same environment. That is a subject which involves various things; for example, time. If a man is in a particular environment, such as a forest, during the day, while the mosquito, which is capable of transmitting a particular virus, is flying and biting only at night, then the two, although they have been in the same three-dimensional space, have not been sharing the space in point of time.

Furthermore, and this is one of the important components in such a situation, particularly in the forest, certain species of mosquito may inhabit the leafy canopy high above the forest floor, while the man goes on foot down below. The two do not share the same environment, although they might appear to do so.

The epidemiologist needs to know quantitatively what these balances are. He needs to be able to determine how long a given species of mosquito may live, how far it may fly, or whether other forces operate to carry it from point to point. In other words, he needs to put a tag on the mosquito itself. It is easier to put a tag on the animal. It can be caught, tagged, tattooed, or something of the sort. But tagging the insect, in nature especially, is a superlatively difficult problem, or was prior to the advent of radioisotopes.

The usual methods which have been employed have been of this kind: an entomologist with abundant help goes out and hand catches as many mosquitoes as he can succeed in getting, blows bronzing powders or dusts on them, and then releases them. Naturally with this procedure, the numbers are limited. The delicate insects have been manhandled. There is always the problem of later recognition of mosquitoes marked in this manner. The dilution in nature is such that one should deal with thousands and millions of insects rather than with hundreds.

Now, it so happens that with a mosquito the complex physiology and anatomy of the small beast is such as to lend itself beautifully to the identification of the individual insect by means of isotopic tagging. Through our discussions, we have talked about the identification of a molecule within an animal, or of following the course of a substance, and we have not brought to your attention that in introducing the radioactive material into the animal, we have distinctly marked the animal as a whole.

It so happens that the mosquito passes through a complicated anatomical situation beginning with the hatching of the egg. The little larva—which is familiar to everyone, I believe, as the little wiggle tail one finds in stagnant pools of water—after passing through a number of stages, undergoes that remarkable change known as pupation, in which it becomes anatomically quiescent externally and changes shape. You will find the mosquito pupae are small dark bodies but still wiggling and moving around. After a few days in that state there has occurred a complete rebuilding of the anatomical structure of the mosquito from the larval form to the adult. The pupal case splits, and there emerges, completely developed and usually beautifully formed, the adult mosquito.

During that remarkable reorganization of the anatomy of the insect, many substances which have been taken up in the larval form are still retained. They are not lost. They go into the building of the adult insect and thereafter remain with it. It so happens that many of the easily used radioisotopes do enter into that type of physiological and anatomical change.

There is in the body of the adult mosquito a peculiar gland, if we may call it a gland, vaguely analogous to a kidney in a mammal, which apparently has something to do with calcium metabolism; and for that reason one can use radiostrontium as a very effective marking agent. It has only to be put in the water in which the mosquito larvae are developing. It will be picked up with great avidity, concentrated in this organ, will pass through the pupal stage, and will be found permanently in the adult mosquito.

Not only can one mark wild mosquitoes easily, simply by putting an isotope in the nutrient of the larvae, but also one finds that every mosquito emerging from that breeding pool will be permanently identifiable with a Geiger counter, and will carry throughout the rest of its life enough radioactivity to be detected externally, although it will not affect the behavior of the insect in the slightest.

What can be done with that sort of thing? One obvious application is in the estimation of the number of individuals of a species in a particular locality. If we release a known number of marked mosquitoes, and allow time for mixing of the populations, by catching representative samples and counting those that are radioactive and the ones that are not, we can determine how many mosquitoes of that species are present.

By making catches with reference to the breeding point, we have at hand the means of determining how far they move, and thus have one of the important factors in the progress of any contagion which has to do with insect transmission, that is, the moving of the infectious agent, the virus of the disease, from one point to another, at times literally with the speed of the wind. And it does develop that in many species of mosquitoes it is wind transport that may be the means by which the disease is actually disseminated.

Of course, that reminds one of some of Dr. Geiling's remarks, that many of these things go back into early history when it was noted, for example, that downwind from swampy areas malaria was a common thing to be found among the population. It was attributed to the mists which arise from the swamps, but in fact was due to the wind transport of anopheles mosquitoes.

Now, if I may further demonstrate this: I brought along with me—I see they are still alive—some mosquitoes which happen to be *Aedes aegypti*, the classical vector of yellow fevor. This is the species of mosquito that was demonstrated by Walter Reed at Havana to be the effective means of transmitting the disease from man to man.

Since that time, the complexity of the epidemiology has been more strikingly shown, and it is realized that not only is there that special cycle, but in the tropical jungles of South America and Africa there is a cycle that goes on between forest mosquitoes and forest animals, particularly monkeys, and into that cycle man may intrude, and then later, in his communities, give rise to the classical epidemic cycle as well.

I am not sure which of these tubes has the marked one, but apparently it is not this, so it could be the other one.

The culprit, you see, was hiding up under the cap, here.

The radiostrontium, a beta emitter of considerable energy, shoots off electrons from the mosquito, and many of those are caught in the plastic tube and do not come through, but the more energetic ones do. So that is the 1 culprit of the 2. These others are essentially normal. They are still alive, as you will notice, and here is a lens, which will show the very nice structure which can be seen on them.

Such simple techniques can be applied in highly diverse circumstances for the purpose of determining where the weak links in the transmission of a given disease may be. For example, with this mosquito, it was possible to show that it is the wind which is the most important factor in carrying it from place to place, rather than the ability of the mosquito itself to fly. In other circumstances, modifying factors may occur of considerable magnitude.

Observations of this type may make it possible to plan a system of control which is based on sound information, and thus effectively to solve a problem which may be, by its very magnitude, one of pressing importance for large populations.

Representative HINSHAW. Has any experiment been made—I presume it has—to determine how far these mosquitoes can be carried by the wind?

Dr. BUGHER. That is one of the things that still has to be done on a more extensive scale. This particular species has been recovered 2½ and 3 miles from its point of release as a young mosquito.

Representative HINSHAW. Then killing all the mosquitoes in one backyard is not going to affect the house very much, is it?

Dr. BUGHER. It may not affect it too much, but there are certain species which lie or hide in the shrubs and may not move very far. So that you do find that there is a practical reasonable limit beyond which the mosquito is not going to move, and if you can destroy all of those within that area, and you remain in the center, considerable freedom from discomfort can arise.

It is the identification of precise quantitative characteristics that means so much in this general field. A good example of that is the control of sleeping sickness. Through the observation that the larva of a tsetse fly would die if exposed to a temperature of 105° F. for 30 minutes, a complete system of control—it was an extremely simple one, since the larvae always develop along a water course in the sandy soil at the edge of the water—was to cut away the trees and let the hot noontime tropical sun beat down on the little stream. By that

simple mechanism, a large area of country was freed from tsetse flies, freed from sleeping sickness, and a complete revolution in the health and welfare of the people was achieved.

Representative HINSHAW. I visited Africa last year. They did not explain in that detail, but they did say that the tsetse fly bred in the trees along the water courses, and that it was a very simple matter to eradicate them. Now you have explained the rest of it.

Dr. BUGHER. That one small fact, which was observed by one of the British entomologists, led to a practical control.

So in this whole problem of the alleviation of disease in underprivileged populations, where public health must be carried on within the economic capability of the people and the social structure of the country, it becomes most vital to determine where and in what way a disease cycle can be broken.

One of the very significant places for the application of nuclear techniques lies in what is really this international medical field of epidemiology with relation outstandingly to the various tropical infectious diseases.

I am very pleased to bring these along as an example of the sort of tagging of the individual which can be made with isotopes.

Representative HINSHAW. That is tagging with strontium 90 in the water in which the larva developed, became a pupa and emerged as the final little beastie?

Dr. BUGHER. Yes. That is the process here. And it all goes back to the fundamental problem that there are critical concentrations of population, both of the mammalian host and the insect vector, below which an epidemic cannot be sustained. In other words, for the eradication of malaria, it may not be necessary to eliminate the last anopheles mosquito. It may be essential only to drop the population of mosquitoes to a certain level. And those are the things that must be measured before one can plan a really practical scheme of control.

Representative HINSHAW. Dr. Bugher, you have lived around here some little time, and we have a little problem in this vicinity known as the chigger. Is anything being done about chiggers? I do not know whether they transmit disease or not, but I do know that they are very pestiferous little beasties.

Dr. BUGHER. In some parts of the world they do transmit disease.

Representative HINSHAW. I have never seen one, mind you, but I have had plenty of contact with them.

Dr. BUGHER. The ones that do the biting are the larvae in this case, and the adults are usually found either in the soil or sometimes around the bark of trees. Some of the most outstanding species are found in the soil as far as the adults are concerned. And after the eggs are laid and the larvae emerge, they seek a single blood meal, either from an animal or a bird or man, and after having obtained that blood meal, they drop off and go through the rest of their development period. So that any infection which a chigger will transmit must be capable of transmission through the egg and the adult, because in a cycle only one bite is given.

They may be destroyed by many different things. The common mosquito repellents are usually pretty good. Even ordinary soap is most effective against their crawling across the skin.

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Representative HINSHAW. Have you ever seen one? I have never seen one, but I have been bitten a thousand times.

Dr. BUGHER. Yes. The larvae are very small in most cases, just about the limit of vision, but they are small red structures which are quite capable of burrowing into the skin. The adults are usually much larger.

Representative HINSHAW. They do not stay there, do they?

Dr. BUGHER. For a short time. Usually in man the larvae do not succeed in establishing themselves too well. They commonly die in the skin and give rise to even greater irritation. They also can be tagged.

Representative HINSHAW. Well, we thank you very much for this remarkable demonstration of how the insects can be tagged. I did not realize that they themselves could be tagged. I thought it was the stuff that they ingested.

STATEMENT OF DR. G. BURROUGHS MIDER, ASSOCIATE DIRECTOR IN CHARGE OF RESEARCH, NATIONAL CANCER INSTITUTE, NATIONAL INSTITUTES OF HEALTH, BETHESDA, MD.

Representative HINSHAW. Now we have a very interesting discussion coming up of tracer techniques and their impact on cancer therapy by Dr. G. Burroughs Mider, Associate Director in Charge of Research at the National Cancer Institute, National Institutes of Health, Bethesda, Md.

Dr. Mider was born in Windsor, N. Y., in 1907, and received his medical degree from Cornell University in 1933. He served as intern and resident surgeon at the Albany (N. Y.) Hospital, and he continued his surgical studies as assistant resident surgeon at the school of medicine and dentistry at the University of Rochester in 1936 and 1937, and then served as a fellow and instructor. In 1938, he was appointed a National Cancer Institute research fellow and assigned to the University of Rochester. When the National Cancer Institute building was completed in 1939 Dr. Mider became a member of the research staff. He continued in cancer research until 1941, when he became instructor in pathology at the Medical College of Cornell University. He was made assistant professor the next year and remained at Cornell until 1944. In 1944 he joined the faculty of the medical school of the University of Virginia as associate professor of pathology. In 1945 Dr. Mider was appointed to the faculty of the school of medicine and dentistry at the University of Rochester as research associate, and in 1948 he became professor of cancer research and coordinator of cancer teaching. He was appointed Scientific Director of the National Cancer Institute in 1952.

The Institute is very fortunate in having the services of Dr. Mider, and we are correspondingly fortunate in having him present the subject of tracer techniques before this group.

Dr. Mider.

Dr. MIDER. Mr. Chairman and gentlemen, I certainly want to state how privileged I feel to participate in these hearings and to have contact with the speakers who appeared earlier in the afternoon.

I should like to make a few remarks which may help to illustrate the nonmilitary use of an important byproduct of atomic science—the use of radioisotopes in the study of cancer. What I have to say will be a little different from the earlier types of presentation.

Scientific investigation operates in a way quite similar to the chain-reacting pile, in which one reaction sets off others in purposeful series to achieve a desired result. The stepwise development of atomic energy to practical reality can be identified with certain individuals. A much larger group of scientists, however, provided essential background information over many years. Scientific research is always a cooperative enterprise. Ideas are born in individual minds, but their formulation is influenced by a wide variety of contacts and their translation into practical reality is aided by the entire scientific community.

The availability of radioactive isotopes has had an enormous influence in biology and medicine, of which cancer research is an extensive and important part. Some of the complex interrelations of the organs and tissues of the body have been defined throughout the centuries, but the advent of isotopes has allowed investigators to establish new concepts of interplay among important body constituents, such as proteins, fats, carbohydrates, minerals, and water. These compounds seem to be in a state of dynamic equilibrium with one another, their utilization closely integrated to serve the needs of the body.

The animal organism frequently has several means of accomplishing a given result. The situation is analogous to sailing a ship. Every part of the ship contributes to its efficiency, and changes in force or direction of wind require adjustments by which a new equilibrium is achieved. The skipper has several options for a given set of conditions, though selection of other than the best course means some sacrifice of speed, comfort, or maneuverability. Optimal and alternative pathways for the formation of constituents of the body are being defined precisely by numerous biochemists, whose results are critically important in the research attack on cancer.

Sufficient progress has been made to increase the therapeutic capacity of practicing physicians. I should like to recount briefly a part of this progress in which availability of radioactive phosphorus (P_{32}) and radioactive carbon (C_{14}) has been crucial. The story illustrates how basic studies of cell chemistry contributed to the continuing development of drugs that are useful in the management of cancer.

Nucleic acid plays an important, probably fundamental part in processes of cellular growth, including synthesis of protoplasm, the essential substance of living tissues. The precise mode of action, however, has never been satisfactorily explained. Two general types of nucleic acids are recognized, according to the type of sugar they contain—either ribose or desoxyribose. It was originally thought that ribonucleic acid, RNA, was characteristic of yeast cells and plant tissues. This idea had to be discarded in light of additional information derived largely from studies using isotopes.

Since all nucleic acids contain phosphorus, radioactive phosphorus (p^{32}) may be used as a tag for the study of their synthesis and utilization in the body—in a word, their metabolism. One approach is to administer labeled phosphorus to a mouse, sacrifice the animal after a suitable period, extract from the tissues the phosphorus not bound

in nucleic acid, and measure the remainder. Workers at the University of California showed that more radioactive phosphorus was incorporated into the tissues of leukemic than of normal mice, and scientists at the University of Wisconsin obtained similar data from rats bearing cancers of the liver. The increased avidity of cancer cells for radiophosphorus proved not to be a specific characteristic of the malignant state, since it was shared by rapidly growing normal tissues such as regenerating liver.

Investigators in Stockholm and at Harvard made an important advance by determining the relative uptakes of radiophosphorus by the two different classes of nucleic acids. The content of DNA was found to be reasonably constant in each type of cell in a given species, whereas the RNA content was subject to such variables as age, starvation, and growth rate. Fractionation of cells into their component parts has confirmed the observation that DNA resides only in the nucleus. RNA also occurs in the nucleus, but is located chiefly in the remainder of the cell, the cytoplasm. These findings provide a means of measuring nuclear activity, which is vitally important in cancer research because of the essential role of the nucleus in cell division.

Representative HINSHAW. Now just a moment, Doctor. You have used the term "nucleic acid" and also referred to "nuclear" this and that. Please differentiate, so that we can understand that they are dissimilar substances.

Dr. MIDER. The nucleic acids I speak of, Mr. Chairman, unfortunately bear this term for historical reasons. They do not necessarily have anything to do, or not all of them have anything to do, with the cell nucleus. One type, however, occurs only in the cell nucleus, and the other type occurs both in the nucleus and in the rest of the cell, but principally in the remainder of the cell. The former we call DNA, desoxyribonucleic acid, and the latter, RNA, ribonucleic acid. The nucleus that I am speaking of is the nucleus that lies in the center of or to one side of most cells and has nothing to do with the atomic nucleus.

Representative HINSHAW. That is right. Now we are getting things straight. It has nothing to do with the atomic nucleus.

Dr. MIDER. Nothing to do with the atomic nucleus.

Representative HINSHAW. Or with neutrons or similar substances?

Dr. MIDER. No, sir. Unfortunately, the paucity of the English language is very well exemplified in the terms "nuclei," "nucleic," and "nuclear."

Representative HINSHAW. All right. Please go ahead.

Dr. MIDER. Heightened interest in nucleic acid chemistry also resulted from the discovery of a series of drugs that temporarily halt the progress of some acute leukemias, especially in children. Folic acid, one of the B vitamins, had been proposed as a remedy, but Dr. Sidney Farber, of Boston, observed that administration of folic acid sometimes aggravated the disease. A change was then made in the molecule, in conformance with the principle that slight modifications in the structure of a compound will not necessarily prevent its use in the body, but may radically alter its biological activity. A series of so-called antifolic compounds became available, of which aminopterin is representative. These drugs are useful, though not curative, in the management of some leukemias.

A relation between nucleic acid and the beneficial effect of antifolic drugs was established through studies with radioisotopes. It had been known that the purines which form parts of nucleic-acid molecules—nucleic acid is a very large molecule—can be synthesized from small chemical fragments. This discovery would have been impossible without the use of radioactive carbon, since one cannot discriminate accurately among ordinary carbons donated by different compounds. The information was so precisely obtained that sources of specific carbon atoms in purine were identified as formate, carbon dioxide, and glycine. The antifolic compounds blocked the formation of purines, which requires a derivative of folic acid, and thus prevented the synthesis of nucleic acids.

Another important approach to this problem is being elaborated in cooperative research by the Sloan-Kettering Institute, the Burroughs Wellcome & Co., and the Southern Research Institute. In addition to synthesizing purines, the body can also utilize some pre-formed purines to build nucleic acids.

This material on the right, adenine, is a normal purine, which is a metabolite. It can be used by the body to help build up these much larger important molecules of nucleic acid. The cooperative research venture synthesized this same compound, but replaced the green group of 1 nitrogen and 2 hydrogen atoms with 1 sulfur atom and a hydrogen atom.

Representative HINSHAW. Do I remember enough chemistry to call that ammonia, on the left? Or is NH_3 ammonia?

Mr. MIDER. Yes. We call this an amino group, and this a sulfhydroxyl group.

Now, the body can incorporate, or apparently incorporate, this material, 6-mercaptopurine (exhibit 62, below), into nucleic acid, but the nucleic acid which is formed cannot function as a normal nucleic acid does. That is why we labeled the important group in this compound "green," and in this one "red." Because the situation is very much like a traffic light, when the proper group is here, traffic, or the metabolic processes of the body, flow smoothly, but a red light flags traffic down and may stop it altogether. So this relatively simple change in chemical configuration of a basic molecule interferes importantly with its biological activity.

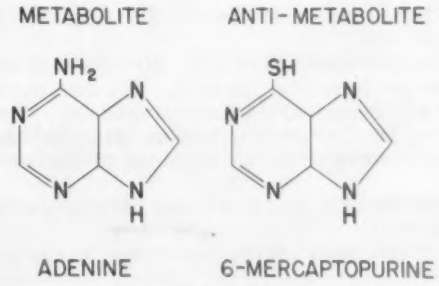

EXHIBIT 62

The 6-mercaptopurine has shown much promise against cancer. Its usefulness has been established, but not the extent of its activity.

Dr. Cornelius P. Rhoads, in a recent discussion called "Rational Cancer Chemotherapy," states that the principles mentioned may "yield new means for cancer control in man within the foreseeable future."

It is fascinating to reflect that the genes, those tiny biological units presumably made up of nucleic acids, may be responsible not only for our individuality but also for individuality at the cellular level. In discussing the application of radioisotopes in cancer research, Dr. Charles Heidelberger wrote:

> The study of the biosynthesis and metabolism of nucleic acids has been made possible almost entirely by the use of isotopes.

Equally interesting developments in the fields of protein synthesis, energy metabolism, and mechanisms by which certain chemicals produce cancer have profited tremendously from the availability of these substances.

This sketchy retrospective summary of one phase of cancer research would be incomplete without acknowledging our debt to the many scientists whose contributions were not motivated by a desire to conquer disease. The study of bacteria, yeasts and molds, for example, has added materially to our medical knowledge and technology. The same can be said of basic explorations in atomic physics. Intellectual curiosity is a potent force in the inexorable advance of science, which sometimes proceeds like Hugh Walpole's three princes of Serendip, who were always discovering, in their travels, things they did not seek. Up until a few years ago, no one could have predicted the course that cancer research would take, but appropriate tools, techniques, talent, and freedom of communication continue to add chapters to the brilliant history of scientific achievement for the benefit of mankind.

Thank you, Mr. Chairman.

Representative HINSHAW. That is a very fine exposition of the present state of that portion of the art, certainly, or the science that is connected with it, and we are delighted to have it for this record. We thank you for the very interesting discussion concerning the use of radioactive tracers in the cancer research program at the National Institutes of Health.

Dr. MIDER. You will be most welcome, sir.

Representative HINSHAW. We have been across the way in the Bethesda Hospital of the Navy. Every Member of Congress is required to go out there by Dr. Calver every so often and get a checkup. But when we see all those beautiful buildings: Are they the ones in which you work?

Dr. MIDER. They are, sir, and you and all the Members of Congress will be most welcome.

Representative HINSHAW. Well, now, we have seen them across the way, but we have not been in yet to visit. We must make an appointment to do that, Mr. Heller, at the first opportunity.

Now, you know, Dr. Calver can chase us out to Bethesda by worrying us. Can't you worry us a little bit more, so that we will go across the street?

Dr. MIDER. We thought you had about all the worries you would like to have, sir.

Representative HINSHAW. Well, Dr. Calver gives us a few extra ones.

Dr. MIDER. But if I get after Mr. Heller, perhaps we can arrange a visit.

Representative HINSHAW. Good. We thank you very much indeed for this fine presentation and shall hope to make that visit in the very near future.

STATEMENT OF DR. SEYMOUR KETY, ASSOCIATE DIRECTOR FOR RESEARCH, NATIONAL INSTITUTE OF MENTAL HEALTH AND NATIONAL INSTITUTE OF NEUROLOGICAL DISEASES AND BLINDNESS, NATIONAL INSTITUTES OF HEALTH, BETHESDA, MD.

Representative HINSHAW. Dr. Seymour Kety will speak on the subject of Employing Radioactive Tracers in the Study of Chronic Disease. He is Associate Director in charge of research of the National Institute of Mental Health and the National Institute of Neurological Diseases and Blindness of the National Institutes of Health in Bethesda, Md.

Dr. Kety has headed the joint laboratory research program of the National Institute of Mental Health and the National Institute of Neurological Diseases and Blindness since 1951.

Best known for his research on cerebral circulation, he has also investigated the mechanisms of anesthesia, psychoses of senility, and the physiological aspects of current treatments for mental illness. He has been cited for his work on the measurement of blood flow and oxygen consumption of the human brain by the American Association for the Advancement of Science, having received the Theobald Smith award for research in the medical sciences in 1949.

Dr. Kety is also professor of clinical physiology at the University of Pennsylvania Graduate School of Medicine and has lectured at the Sherrington School of Physiology in London, England, and the hospital de la Salpetriere in Paris.

He has been special consultant in physiology to the United States Air Force and is on the research council of the National Multiple Sclerosis Society and the research advisory board of the United Cerebral Palsy Associations. He has contributed to professional journals a number of scientific articles on cerebral circulation, metabolism, and inert gas exchange.

He has been a member of the editorial board of the Journal of Pharmacology and Experimental Therapeutics. His professional affiliations include the American Academy of Neurology, the American Society for Clinical Investigation, the American Physiological Society, the American Society for Pharmacology and Experimental Therapeutics.

Dr. Kety, age 39, received his doctorate of medicine degree from the University of Pennsylvania in 1940.

Dr. Kety, we shall be delighted and honored to hear you.

Dr. KETY. Thank you, Mr. Chairman.

For the past 15 years, the research of myself and my colleagues has been bountifully facilitated by the opportunities which atomic energy has provided to us, and I consider it a personal privilege to appear here this afternoon to indicate my debt as well as the debt of all of medical science to this phenomenal discovery.

Our knowledge of the causes, detection, prevention, and cure of disease develops by process of careful search and cultivation, and occasionally by an unprecedented leap. Such leaps were the in-

vention of the microscope around 1600, the discovery of micro-organisms as causes of disease, and in our own times, the application of atomic energy to medical research and treatment.

I shall attempt to describe in a general way the impact of the tools and techniques made available by atomic energy on the major chronic diseases other than cancer, which is being discussed by others at these hearings. Although in a few instances, practical, lifesaving results have already been achieved, the contribution in the majority of cases has been to our basic understanding of these diseases—a process which usually precedes and forms the foundation of major practical advances.

Diseases of the heart constitute the major cause of death today, and among these the greatest offender is arteriosclerosis. Much has been learned about this disorder in the past few years by the use of isotopic techniques. It is now know, for example, that cholesterol, a fat-like substance which forms the bulk of the abnormal deposit in blood vessel walls, far from being an inert substance as formerly believed, is in a process of rapid turnover within the body, entering by way of the diet to some extent but, equally important, capable of being synthesized by the body itself. The problem of effective treatment may be approached more fruitfully by an attack on the abnormalities of synthesis and deposition than by attempts to dissolve the material already laid down.

Heart failure is the cause of untold incapacitation. Studies on its etiology and pathogenesis are being actively pursued—studies made possible by the use of isotopes of sodium, chlorine, and hydrogen for investigating salt and water exchange and the role of the kidney in its regulation——

Representative HINSHAW. Doctor, this is going to be read, we hope, by a great many thousand people, and the terms "etiology" and "pathogenesis" ought to be spelled out a little bit so that it is readable and understandable to the ordinary person who runs and reads.

Can you define them?

Dr. KETY. I shall be glad to.

Etiology is a term which embraces the causes of disease, and pathogenesis includes the manner by which a disease operates to produce its damage and deleterious effects in the body.

Representative HINSHAW. Very good, sir.

Dr. KETY. Scientists have used isotopes of iodine, iron, and chromium for studying the blood volume; and other isotopic techniques for measuring the flow of blood.

Radioactive isotopes, in addition to aiding progress in heart research, have proved useful in the management of certain heart patients. Thyrotoxic heart disease—now one of the most curable of heart conditions—can be successfully treated by doses of radioactive iodine. This condition is due to an overactive thyroid gland, or hyperthyroidism, which speeds up the fuel consumption of the body and consequently its oxygen requirements. The heart, pumping more blood at a faster rate to meet these oxygen demands, may enlarge, may beat too rapidly or irregularly, or may fail. The cardiac output in a thyrotoxic patient when he is at rest is equivalent to that of a normal person occupied with light work—but work continuing 24 hours a day. Administration of radioactive iodine provides not only a means of diagnosis, but also a simple, effective, and often curative treatment.

The same principle has been applied in the treatment of patients with angina pectoris or congestive heart failure who do not respond to other available measures and remain incapacitated and in severe discomfort. Radioactive iodine therapy has brought considerable improvement to some of these persons. This occurs because the isotope acts to reduce the activity of the normal thyroid gland, thereby lowering the total metabolism of the body to within the limits of the heart's capacity.

Representative HINSHAW. Now, Doctor, you could accomplish the same effect by the use of ordinary iodine, but you use the radioactive isotope for purposes, I presume, of clinical analysis and diagnosis, and so forth. Is that correct?

Dr. KETY. Not quite, sir. It is perfectly true that ordinary iodine will cause a temporary remission in patients with hyperthyroidism, although ordinary iodine will not affect the thyroid of a normal individual. However, even in patients with overactive thyroids, the efficacy of inert iodine treatment is exerted for only a period of a few weeks, after which time it becomes ineffective.

The function of radioactive iodine is inherent not only in its peculiar ability to be picked up selectively by the thyroid and concentrated there above its concentration in any other tissue in the body, but, more important, by its radioactivity, subjecting the thyroid cells to continuous bombardment and eventually destroying the function of these cells. So that the radioactivity is an essential feature of this type of therapy, and without it, it would not be efficacious.

Representative HINSHAW. Well, the radio treatment forms one part of it, but the fact that it is an isotope—it might or might not be radioactive—does the other part of the job. Is that right?

Dr. KETY. Well, the fact that it is iodine is important, because any other isotope would not be selectively picked up by the thyroid. And the fact that it is radioactive is important, because the radioactivity kills the thyroid cells.

Representative HINSHAW. Yes, but you said a moment ago that inert iodine did not do the job.

Dr. KETY. Inert iodine, for a reason that we don't quite understand, seems to pacify the overactive thyroid for a very short period.

Representative HINSHAW. Well, I was just thinking that it ought to be related somehow to the fact that the isotope is of a different atomic number.

Dr. KETY. That is an interesting suggestion, but I don't believe there is any evidence to suggest that the thyroid can distinguish between the isotopes of iodine.

Representative HINSHAW. Well, you have got a clinical difference. Now you had better find out why.

Dr. KETY. Well, sir, it is because of the radioactivity.

Representative HINSHAW. Only?

Dr. KETY. Yes.

Representative HINSHAW. All right.

Dr. KETY. The thyroid is only one of many endocrine or hormone-producing glands which are important to health or survival. Among the metabolic diseases, the most important is diabetes mellitus, a disturbance in glucose utilization resulting from an actual or relative lack of insulin. It is now possible to tag this hormone of the pancreas

by means of an isotopic label, opening up to investigators what hitherto have been the profound mysteries of where and how it acts in the body.

The important hormones of the adrenal cortex have recently been shown by means of isotopic techniques to be formed from cholesterol. Within the past year the important adrenal steroid, cortisone, and two closely related compounds have been isotopically labeled, and studies are underway to determine their metabolism and the mechanisms by which they act to relieve the symptoms of many forms of arthritis.

Two other hormonal agents, epinephrine and serotonin—of possible importance in hypertension, anxiety, and some forms of mental disease—are being subjected to exhaustive research by means of radioactive techniques, which have already delineated the pathways and rates of their formation and destruction in the body.

Our understanding of the various forms of anemia has been tremendously broadened within the past decade as a result of isotopic techniques for labeling red blood cells in order to study their formation, survival, and destruction. Results of inestimable practical value in the treatment of military and civilian casualties have been made possible by the application of isotopic techniques to problems of the safe handling of blood for transfusions and the development of adequate blood substitutes. The savings in this field alone may well be expressed in thousands of lives and millions of dollars.

Various isotopic substances permit investigation of the intricate processes by which micro-organisms multiply, the enzyme systems essential to their functioning, their response to foreign substances, and the ways by which they distort the chemical processes that take place in the microscopic confines of infected cells. Without use of tagged materials, it would be difficult to map the metabolic systems and to arrive at an understanding of how micro-organisms actually function and produce disease.

The importance of radioisotopes can be illustrated by studies now underway concerning the phenomenon of bacterial resistance to the antibiotic drugs. The answers to this problem depend largely on the extension of our present meager knowledge of the precise mode of action of these drugs. Fundamental to this is the need for better understanding of the life processes of the micro-organisms against which the antibiotics are employed.

In the same way, it is possible to study the behavior of micro-organisms in the presence of antibiotics and to determine how these drugs affect normal metabolism. An understanding of how antibiotics such as penicillin and aureomycin interfere with the growth of micro-organisms is a prerequisite to discovering how some of these organisms are able to alter their life processes and to develop resistance to once-lethal drugs. Such studies require highly sensitive techniques. Without the use of radioisotopes, it would be impossible to measure minute amounts of antibiotics and to follow their course in the metabolic pathways of micro-organisms.

Radioactive isotopes find outstanding usefulness in studies of mineral metabolism and the effects of trace elements in the body. They have already contributed significantly to our understanding of the formation of teeth and bone and to the interesting role of flourine in calcium metabolism and the prevention of dental caries. Studies

with radioactive isotopes of lead, arsenic, and other toxic metals have clarified their mechanisms of transport and excretion, and have contributed to the present effective treatment of heavy-metal poisoning.

In nervous and mental diseases, the costliest of all in terms of public funds and human resources, the basic and applied contributions made possible by isotopic techniques indicate their essential role in our future understanding of these disorders. Within the past few years a major and fundamental advance has been the discovery of the means by which the electrical pulses which mediate all the activity of the nervous system are produced. It has been shown that these impulses are the result of the differential movement of sodium and potassium ions into and out of the nerve cell. This process, occurring within a few thousandths of a second and involving only a few billionths of a gram of potassium or sodium per impulse, could not have been elucidated without the beautifully sensitive techniques for detection and analysis which atomic energy and radioactive isotopes afford. Similarly, research on the causes of muscular dystrophy has demonstrated, by means of isotopes of potassium, an inability of these diseased muscle cells to retain their normal share of the potassium ion.

For the first time, certain radioactive gases are enabling investigators to measure the circulation to the brain during the tremendous accelerations of supersonic flight, where pilot blackout is the important human limiting factor.

I may amplify upon this for a moment, if you will permit me, to indicate that the unique and remarkable advantage of radioactive isotopes in this connection is that by means of their gamma rays they permit detection and analysis outside the body without disturbing the normal human brain. So that by permitting a subject to inhale radioactive gases, one has a means of measuring the uptake of these gases by the brain. This uptake by the brain is a function of the rate at which blood flows to the brain, and studies are underway by which it is possible to learn what is the cerebral circulation under these tremendous gravitational stresses to which our fliers are being subjected.

Techniques which permit the tracing of these gases and many other substances within the brain, by virtue of their radioactive properties alone, are yielding information basic to our understanding of such vital problems as the senile psychoses, cerebral palsy, and epilepsy, and such phenomena as coma, sleep, and anesthesia.

The localization of brain tumors, so faulty at best, and so critical to the neurosurgeon attempting to save the life of the patient, has been greatly facilitated by the use of compounds tagged with radioisotopes—iodine and phosphorus, among others—which are selectively concentrated by certain tumors, thus revealing themselves and their position to sensitive detecting instruments.

I have tried to suggest the impact of one of the most significant contributions to medical progress of all time, and to convey to you only a few examples of the hundreds of advances which have been made and, I am sure, will continue to be made, in our understanding of every important disease, through the application of atomic energy and its product to medical science.

Thank you.

Representative HINSHAW. We think you very much, Doctor. It has widened the thinking of all of us very materially to have these

remarks of yours, and we note that you also are located out here in Bethesda, right across the way from our biennial place of business, the Bethesda Naval Hospital, and perhaps we can be persuaded to come across the street sometime and visit you, too.

Dr. KETY. I hope that that will be possible, sir. I join Dr. Mider in extending a most cordial invitation.

Representative HINSHAW. My young friend has inquired: What is senile psychosis?

Dr. KETY. That is a term which is used to designate the mental aberration which occurs in some individuals as they grow old. It does not occur in every elderly individual, and there are in this country today, fortunately, a large number of elderly people whose mental acuity is just as keen as it was in their younger years. However, in a fairly high percentage of elderly people there does appear evidence of mental deterioration, and it is that group of conditions which is designated as the psychoses of senility.

Representative HINSHAW. Now, are you attempting, in your studies, to correlate the activity of the hormones secreted by the various glands, to find what a normal balance is in the normal person by the use of tracer elements?

Dr. KETY. Those are many of the studies which other investigators are performing at the National Institutes of Health and throughout the country.

Unfortunately, my own research is not along those particular lines. But that is the type of work which is being done in the field of the hormones and their metabolism.

Representative HINSHAW. Has any effort been made to determine whether the natural hormone as extracted in the packing plants or at least partly in the packing plants and later refined, is more or less effective, or more or less efficacious, let us say, than the synthetic hormone, the synthesized hormone?

Dr. KETY. Well, sir, in only a few instances have the biochemists been fortunate enough to be able to synthesize hormones. The hormones of the adrenal cortex and medulla are capable to some extent of synthesis at the present time.

Cortisone is an example of one of those.

The hormones of the pituitary are not capable of synthesis, except that recently a hormone of the posterior pituitary has been synthesized by Dr. Duvigneaud in New York. The hormone of the thyroid, of the parathyroids, are still not completely susceptible to synthesis. However, with respect to those where synthetic hormones are available, such as those of the adrenal cortex, I think it is fair to say that evidence suggests that the naturally occurring hormones are still more potent than those which have been synthesized. And I believe that that is because we have not yet synthesized the complete spectrum of hormones which are available from the adrenal cortex, but have succeeded only in relatively few, whereas the adrenal cortex probably produces about 50 hormones.

We have succeeded, or biochemists have succeeded, in isolating or synthesizing only a handful.

Representative HINSHAW. I am asking for information now.

Is it true that there are German patents which have been exercised in the manufacture of the so-called sex hormones?

Dr. KETY. One of the most potent of the sex hormones, testosterone, was, I believe, isolated and analyzed by Butenandt in Germany, and, I believe synthesized by Ruzicka in Switzerland. I suppose the Swiss Government had patents on that synthesis for a while.

I believe that testosterone is synthesized in this country by a number of pharmaceutical firms. How the patent laws apply is beyond my field.

Representative HINSHAW. I was not concerned so much about the patent laws as I was about the process; that is, whether it has become a commercial process, and whether it is known yet as to the relative effectiveness or deleterious effects that may be had from it.

Dr. KETY. I had the good fortune of working with Dr. Aub in Boston some 8 years ago, and he and I wrote a review on the subject of testosterone.

It is my impression from that study that testosterone, synthetic testosterone, is fully effective in relieving certain of the symptoms of testicular deficiency. However, it does not, by any means, cause a restitution which had been claimed for that type of therapy in former years.

Representative HINSHAW. We wish to thank Dr. Seymour S. Kety for his presentation here today.

The hearings are adjourned until 2 o'clock tomorrow.

(Whereupon, at 4:30 p. m., Thursday, June 3, 1954, the hearing was adjourned until 2 p. m., Friday, June 4, 1954.)

THE CONTRIBUTION OF ATOMIC ENERGY TO MEDICINE

FRIDAY, JUNE 4, 1954

CONGRESS OF THE UNITED STATES,
JOINT COMMITTEE ON ATOMIC ENERGY,
SUBCOMMITTEE ON RESEARCH AND DEVELOPMENT,
Washington, D. C.

The subcommittee met, pursuant to recess, at 2 p. m., in the caucus room, Old House Office Building, Hon. Carl Hinshaw, chairman of the subcommittee, presiding.

Present: Representatives Hinshaw and A. L. Miller, of Nebraska; Edward L. Heller, professional staff member.

Representative HINSHAW. The committee will come to order.

We have with us on the stand today Dr. A. L. Miller, a Member of Congress from Kimball, Nebr., who is a medical doctor, having received his medical doctorate degree from Loyola University of Chicago, Ill. He is a life member of the American College of Surgeons, and since 1920 used radium in his practice in the treatment of cancer.

We are glad to have you with us, Dr. Miller, sitting here and listening to this important testimony.

I would like to say that this is a continuation, of course, of the hearings which we have been holding the last 3 days on the subject of the use of radioisotopes in the research and treatment in the medical science.

STATEMENT OF DR. CHARLES F. GESCHICKTER, PROFESSOR OF PATHOLOGY, GEORGETOWN MEDICAL SCHOOL, WASHINGTON, D. C.

Representative HINSHAW. We are to hear a discussion of the use of calcium 45 in medical research on arthritis and cancer by Dr. Charles F. Geschickter and his associate, Dr. Benedict Duffy. Dr. Geschickter was born in Washington, D. C. He received his bachelor of arts degree and his master of arts from George Washington University, and doctorate of medicine degree from Johns Hopkins Medical School. He served as resident in medicine in the Baltimore City Hospital from 1927 to 1928, as a fellow at the Mayo Clinic in 1928; director of the pathological laboratory, associate in surgery, and director of the cancer research laboratory at Johns Hopkins from 1929 to 1940. He was director of the Garvan Cancer Research Fund from 1940 to 1946. He saw 5 years of active service as a commander in the Medical Corps of the United States Navy during World War II. He served as chief pathologist with the United States Naval Medical School from 1942 to 1946; as consultant pathologist in the United States Navy Medical Center—I presume in Bethesda—from 1945 to 1948. He was consult-

ant pathologist at the United States Naval Hospital from 1946 to 1948.

Dr. Geschickter was appointed to his present position as professor of pathology at Georgetown University Medical School in 1946. He has served as consultant in pathology in the United States Naval Medical School since 1942, as a consultant in pathology in the Mount Alto Veterans' Hospital since 1946 and as pathologist in chief at the Gallinger Municipal Hospital since 1946. He is a member of the American Medical Association, American Association for the Advancement of Science, the Johns Hopkins Medical and Surgical Society, the Southern Medical Association; he is a member and past president of the American Association for the Study of Neoplastic Diseases, and he is a diplomate of the American Board of Pathology. He has written textbooks on tumors of the bone, diseases of the breast, and diagnosis in daily practice. He is the editor of the United States Navy Color Atlas of Pathology, and has published over 135 articles in the medical field.

With that distinguished record he appears before us to discuss the use of calcium 45 in medical research on arthritis and cancer.

Dr. Geschickter, we are delighted to have you present.

Dr. GESCHICKTER. Thank you very much.

We at Georgetown became interested in calcium 45 because from 1926 until 1946, I had been interested in bone tumors. We thought we would get a new tool for the study of disease of bone and articulating structures if we could learn more about the metabolism of calcium.

Calcium is only one of many essential elements or metabolic substances in the body for which there are radioactive isotopes which can be used for labeling and tracing the turnover in the body fluids and tissues.

When we started with calcium 45, the technique of measurement proved rather difficult because calcium is a beta emitter. While it has a long half life of 6 months, the amount of electron volts emitted are small in comparison with a number of other isotopes. Also, the material we got from Oak Ridge at first was not quite as "hot" or pure as it turned out to be later.

As we went along we learned more in the use of the technique, and also our task became easier as better and better samples became available from Oak Ridge. We were able ultimately to construct curves for the disappearance of radio calcium from the blood after its intravenous injection, or after its administration by stomach tubes into rabbits.

You can see from the chart (exhibit 63, p. 141) here that the blood disappearance rate of calcium 45 follows a definite curve, and this curve is the same (although it appears later), when the material is first put in the gut, and then reaches the blood and begins to disappear.

One of the outstanding advantages of working with isotopes in a medical institution is that it brings to the field of medicine mathematicians and physicists. We were fortunate to have such people working with us. Dr. Litowitz, from the physics department of Catholic University, who is working with us as part-time consultant, was able to analyze these disappearance curves and show that four separate rates were involved in the disappearance of calcium.

From these rates we were able to subsequently account for each 1 of the 4 factors (exhibit 64, p. 141). The first factor which accounts for

the most rapid fall in blood concentration is the so-called compartment factor or diffusion of the calcium away from the blood into the other tissues and fluids of the body.

The second factor is the bone uptake. Within the first 4 hours the bone absorbs practically all that it is going to absorb of the radio calcium. In young animals this constitutes 89 percent of the injected calcium. In old animals it constitutes only about 41 percent.

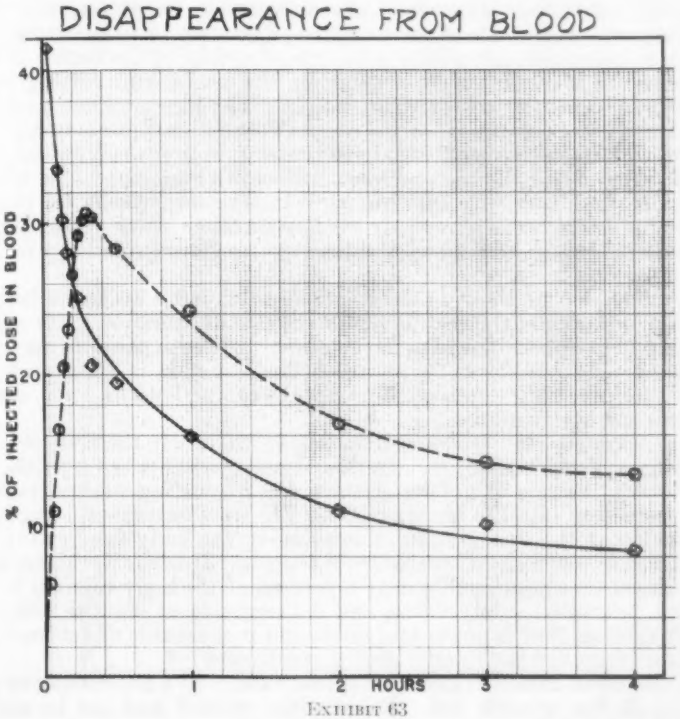

EXHIBIT 63

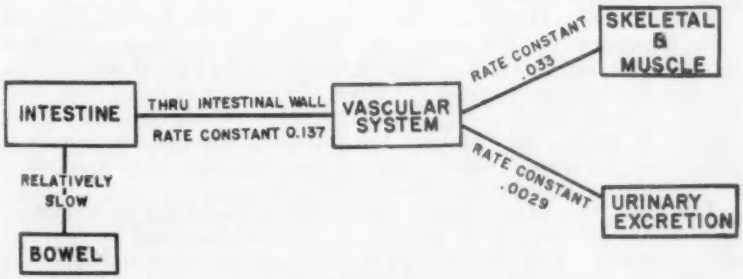

EXHIBIT 64

The slow fall of the blood concentration curves after 2 to 4 hours is due to the excretion of calcium. Fifteen percent of the calcium is excreted by the kidneys into the urine in 24 hours. On the other hand, the excretion into the bowel is only 5 percent and it occurs more slowly.

We were able from these studies to show that by short-term accurate measurements of only 4 hours it is possible to predict the long-term distribution of calcium in the body over a period of days. Second, we were able to show mathematically that bone uptake of calcium in normal individuals is inversely proportionate to the excretion of this substance. If the rate of the excretion of the isotope in the urine and feces is known one can calculate the rate of uptake by the bones. This avoids the necessity of operating on the bones and cutting into healthy tissue to study their metabolism. The feces and urine can be obtained from the animal or individual without harm or trauma.

So with these two facts established we sought to use calcium 45 as a tool for studying disease processes. Since we hesitated to introduce calcium 45 at that time into human beings in large doses for tracer techniques, we went about our studies in other ways. We sought to modify this distribution curve by experimental procedures in our animals.

Here are curves showing the uptake of calcium by the bones for old and young rabbits and here is shown the rate of excretion in the urine (exhibit 65, p. 143) which is inversely proportionate to the rate of bone uptake (exhibit 66, p. 143). The excretion is high in adults and low in young animals. The uptake in the bone is high in the young and low in adults.

In seeking to modify the distribution of calcium in the body we ran into unexpected difficulties. In the normal animal it is very difficult to disturb the rate of uptake by the bones by putting substances into the tissues or into the blood stream. We were surprised, therefore, to find that the distribution of calcium in the body can readily be modified by metabolic disturbances in the gut. In other words, the gut which excretes and handles only 5 percent of the body calcium in 24 hours, is a great safety valve, and it is capable of handling all the body calcium that is put in and more, and it is capable of subtracting calcium from the body under special conditions.

This can be demonstrated by a spinach diet. We put rabbits on an 18- to 21-day spinach diet. Rabbits like spinach and can be maintained indefinitely on it, apparently.

Representative HINSHAW. We ought to call these rabbits Popeyes.

Dr. GESCHICKTER. We will see that the spinach diet does unexpected things. We find that a spinach diet increased the rate at which radio calcium 45 disappeared from the blood stream. You can see on these charts it is definitely low. When we come to analyze where this calcium is going, we find that the increased disappearance rate is not due to the bone uptake. Instead the bone uptake of calcium is lowered under these experimental conditions.

The deposition of calcium in the tissues is depressed by a spinach diet. The urine output of calcium is not much modified by repeated spinach meals. But what occurs is a tremendous intestinal retention and fecal excretion of calcium in the presence of spinach, which has a high percentage of oxalic acid which combines with calcium and represents a reservoir or sponge, which competes with the tissues for

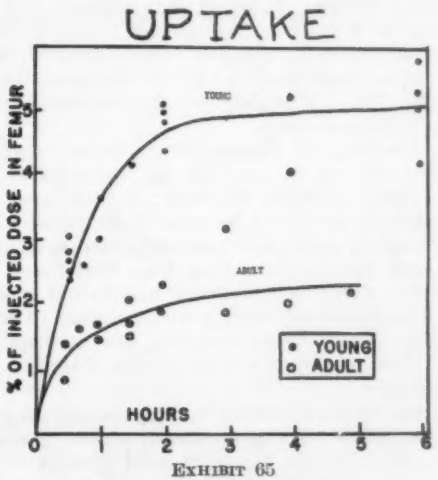

EXHIBIT 65

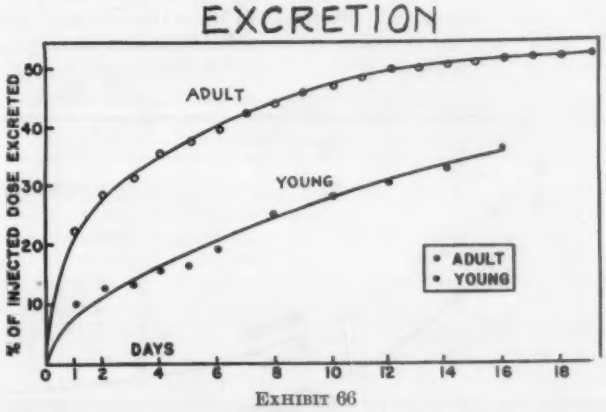

EXHIBIT 66

the uptake of the calcium ion. It tends to pull the calcium through the gut wall into the fecal stream.

We know that in a great many diseases there is an increased or abnormal deposition of calcium in the tissues. Practically 100 percent of the population gets osteoarthritis after the age 45 in varying degrees of severity. The majority of cases do not have the symptomatic form. The disease is characterized by spur formation around the joints. It gives creakiness and eventually painful joints to many people as they get older, especially if they are overweight.

Calcium deposition also occurs in hardening of the arteries or arteriosclerosis. It occurs as brain sand, as we pass through the later years of life. Calcium deposition is also instrumental in the formation of kidney- and gall-stones.

It therefore appeared rather important, and perhaps fruitful, to see whether a spinach diet would influence the symptoms of osteo-

arthritis, in human beings. It is certainly a simple and harmless form of therapy. We have treated a number of cases of osteoarthritis by asking them to eat spinach, whether frozen, canned, or raw, at least once a day, 5 days a week, and to restrict the quantity of eggs, milk, and cheese in the diet. A remarkable improvement occurs in 1 to 2 weeks in many of these patients.

By the way, speaking of Popeye, we find that spinach is a great thing for Popeye, but not so good for his young admirers. (Exhibit 67, below.) It is the old people who won't bother to eat it, that need it. Young people should not eat it because it competes with their bones for calcium. Children need twice as much calcium as adults.

Now, it has been known for a long time that there are substances which make hard water soft. These are called chelating agents. They have the faculty of combining with calcium to form a complex that prevents the calcium from ionizing, but does not precipitate it as a chalk so it does not form a scum in the water to interfere with commercial processes.

Several of these forms of chelating agents known as Versene and sequestrene are available. The technical name is ethylenediaminetetracetic acid. This agent has four acid groups to the molecule. We found that this chemical complexing agent for calcium could be substituted for spinach, and would hold onto the calcium and again depress tissue uptake, increase fecal excretion, and depress urinary excretion. (Exhibit 68, p. 145.)

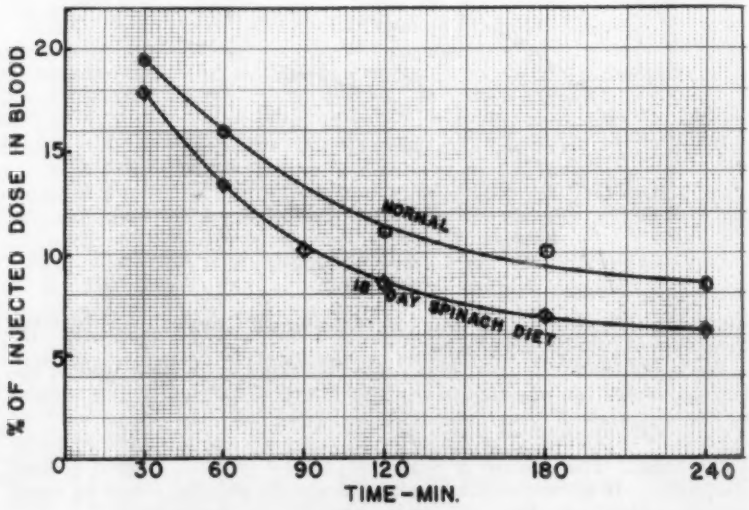

EXHIBIT 67

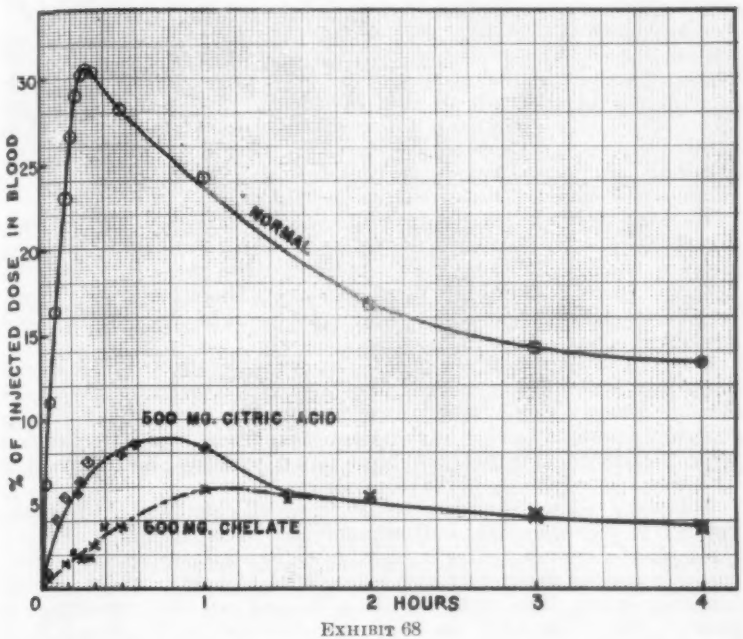

EXHIBIT 68

In the same way magnesium citrate or any of the organic salts of magnesium, if they will combine with calcium on one side of the molecule and exchange magnesium for calcium on the other, act as an agent for depressing the absorption of calcium by the tissues, and in that way tend to reverse the disease process and drain calcium from abnormal deposits.

These agents we have applied to human beings also. We found soon enough that feeding these chelating agents by mouth caused the patient to vomit by taking calcium out of the wall of the stomach. This was overcome by coating the pill with an enteric coating which protects the material from the stomach, but does allow its liberation in the bowel. By this method chelating agents can be substituted for spinach and constitute a little more highbrow form of therapy, with the same decalcifying effect.

Oddly enough, one of the ways of depressing the amount of calcium available to the body is to give an excess in the gut. Any excess of unused calcium in the gut tends to increase the amount that is lost from the body by constituting a reservoir which competes for the exchange of calcium ions in the intestinal wall.

You see here some of the curves of normal absorption of calcium in the gut and these other curves to show its depressed absorption when it is competing with magnesium citric acid or chelating agents such as sequestrene.

One of the unsolved problems of medicine is high blood pressure, which is the greatest killer of citizens of the United States, even

more so than cancer. It gives rise to a combination of diseases of the heart and blood vessels, kidney and brain. The tone of the blood vessels and the way in which a state of contraction of their walls is maintained is a function of the concentration of calcium and magnesium ions. We thought that it would be possible by complexing calcium ions in the blood stream to alter the blood pressure in animals and in patients. If a great deal of the calcium is immobilized in the blood stream, magnesium tends to take its place. Calcium tends to maintain the tone of normal muscular contractions. Magnesium tends to depress that tone and make the muscle flabby.

So what if we can complex calcium and not precipitate it, but inactivate the ions, magnesium will replace it. As the calcium curve goes down in the blood stream, the magnesium curve goes up. When this occurs in patients with high blood pressure or in animals made hypertensive by kidney operations, there is a marked fall of the blood pressure.

So this knowledge of how to complex or inactivate or distribute calcium ions that we first learned about through the generosity of the Atomic Energy Commission in supporting the work and giving us radioactive calcium 45 has enabled us to take patients into the hospital with threatening strokes and high blood pressure, and depress it by lowering the calcium in the blood serum.

It is not a method that you can use very well outside of the hospital, because it occurs quickly and abruptly, and the patient or the animal's blood pressure can be brought down to zero very rapidly. Fortunately you can counteract such a drop with adrenalin, which is sometimes necessary. The method, while of limited practical importance at present, illustrates what has been said over and over again, a little knowledge is a poor thing, but a fundamental understanding of any vital process is an important tool, not only for the present, but for the future.

We were interested in the rate of absorption of calcium 45 and hope in time to supplement studies of calcium 45 with P–32, in measuring another process of the body. This process is the length of life of cells and the rate at which they are renewed. Our work with calcium never progressed to the point where we would measure the life cycles of bone cells. With P–32 the work has progressed a little further.

Other people have worked with radioactive iron and traced the length of life of red blood cells. All I want to do here then is mention that the fundamental fact about cancer is that it only occurs in tissues which are undergoing self-renewal as a normal process. The first sign of the cancer tendency is when this cycle of renewal undergoes modification. The radioactive isotopes by labeling things that the cell uses for its life cycle enable us to determine accurately the length of life of normal cells. We can thus trace the period they consume in time from birth to old age and death, and with a knowledge of this life cycle, we will begin to know mathematically as we have demonstrated here, what actually is taking place in tissues that are falling behind in their attempt to renew themselves, and are thus becoming increasingly susceptible to cancer.

Representative HINSHAW. That is a very remarkable discussion on this very important subject. You have done it in a quite short order. I am sure you could extend it to book length.

Dr. Miller, did you want to ask any questions?

Representative MILLER. It is certainly a challenging and most interesting statement that he has made. It opens up a whole new field. I expect that your researchers will continue to explore, and perhaps eventually come up with the answer as to what can or cannot be done with calcium or boron salts. I was up at Brookhaven a couple of months ago where they were treating some brain tumors of a multiple type with boron and radiating directly after the boron had been injected into the blood stream. There were rather astonishing results.

Is this calcium treated ahead of time?

Dr. GESCHICKTER. The calcium is radioactive as it is split off in the atomic pile. It is not made radioactive after introduction into the body, the way boron is, by neutron bombardment. It is not as strong an emitter of radiant energy as some of the other isotopes. It has been tried as a cancer therapeutic agent in bone tumors. But it does not compare with such substances as gallium because it does not have the punch or radioactive strength.

Representative MILLER. Have you tried any calcium in your metastatic cancers of thyroid?

Dr. GESCHICKTER. Iodine is better there. The only competitor I known of in cancer of the thyroid would be antimony, which also goes to this tissue.

Representative MILLER. Yes.

Dr. GESCHICKTER. Calcium is the great bone seeker and it could be used to bombard bone except for its weakness and the fact that the blood cells are more susceptible and the bone is rather resistant.

Representative HINSHAW. Calcium 45 is the radioactive isotope of calcium?

Dr. GESCHICKTER. Yes.

Representative HINSHAW. You said it had a half life of 6 months?

Dr. GESCHICKTER. About 180 days. It is a nice product. You can ship it from Oak Ridge and get it around the country. It is still very active on arrival.

Representative HINSHAW. It is better for use, I presume than strontium 90?

Dr. GESCHICKTER. Yes.

Representative HINSHAW. On account of the long half life of strontium 90.

Dr. GESCHICKTER. The other thing is that it is a beta emitter. Its rays can be stopped by glass or simple shielding. A calcium 45 laboratory is not a real hot one. Your personnel is relatively safe. When you start dealing with iodine and strontium, you have a real hot laboratory, and your expenses and arrangements are of an entirely different order.

Representative HINSHAW. I was very much interested in your discussion of high blood pressure or hypertension, I believe you call it. You say you can reduce the blood pressure to zero.

Dr. GESCHICKTER. You can do it. Of course, you don't want to. You can reduce it just as precipitously as desired according to the amount of calcium complexing substance you put into the blood. You can measure the drop proportionately to the drop of serum calcium. That is a highly scientific way of lowering blood pressure which we demonstrated and reported. It is probably more scientific than prac-

tical, although it can be used, and we have used it clinically. The doctor must stay at the bedside during the crucial time of treatment.

Representative MILLER. Is it an intravenous injection?

Dr. GESCHICKTER. Yes. You can protect the patient with magnesium ion. Oddly enough, if you give calcium you make them worse under those circumstances.

Representative HINSHAW. Are you able to regulate it continuingly?

Dr. GESCHICKTER. Yes. We have tried it. I do not know that the method should be pursued here too much, but I have applied chelating agent in a cream to the skin. As you lower the blood calcium, the blood pressure falls. So if we could find that method of accurately dosing, you can use it in hypertension.

There again it is a fine method of regulation that we have only tried in desperate cases. There are other methods that are safer and more gentle.

Representative MILLER. One of the big problems of surgery is your calcium and chloride balance when the patient is becoming exhausted from a lack of fluid. If you can keep a nice balance, your patient does all right.

Dr. GESCHICKTER. It is remarkable how this balance follows these mathematical curves. You can get the rate constants for each phase of them.

Representative MILLER. May I ask one more question, Mr. Chairman, about spinach. How did you fall into the spinach experiment?

Dr. GESCHICKTER. I will tell you how we fell into spinach—to avoid a rhubarb. Rhubarb is even more potent in taking out calcium than spinach, they say. We have never tried rhubarb. When I was a boy we had a whole batch of rhubarb, and we had it for supper every night so I dislike it, maybe that is why we chose spinach.

Representative MILLER. Rhubarb and spinach then you think have some effect upon the calcium?

Dr. GESCHICKTER. Yes.

Representative MILLER. Wouldn't it affect blood pressure also? That is, wouldn't it be beneficial in high blood pressure?

Dr. GESCHICKTER. In patients with osteoarthritis, a great many who have mild degrees of high blood pressure, and some severe, you can control the moderate cases and some of the severe ones very satisfactorily with spinach and a magnesium supplement. As you pull out calcium and replace it with magnesium blood pressure may fall. The magnesium protects against calcium deficiency. You can control blood pressure by diet in some cases.

Representative MILLER. Have you anything to offer on cholesterol in the blood?

Dr. GESCHICKTER. We did not measure our cholesterol accurately in these cases. I cannot answer that question as to whether the cholesterol changes under these ionic shifts between calcium and magnesium.

Representative MILLER. Thank you, Mr. Chairman.

Representative HINSHAW. We thank you, Dr. Geschickter, for your presentation here today.

Dr. GESCHICKTER. Thank you, sir.

STATEMENT OF DR. BENEDICT DUFFY, JR., DIRECTOR, RADIOISOTOPE LABORATORY, GEORGETOWN UNIVERSITY, WASHINGTON, D. C.

Representative HINSHAW. We have Dr. Benedict Duffy, who is working with Dr. Geschickter, to continue the discussion. He is a graduate of Princeton University and received his M. D. degree from the University of Rochester in 1944. He saw active duty with the United States Navy during World War II, in 1945–46 and again in 1953. Dr. Duffy took graduate training at the United States Naval Hospital in Brooklyn, N. Y., in 1945, at the University of Illinois Research Hospital in 1946, and at the Memorial Hospital in New York City from 1947 through 1950. He served as instructor in medicine at the Cornell Medical School from 1948–50; as instructor in medicine and radiology at the Rochester Medical School from 1950–53. During this period, he also served as an associate at the atomic energy project at the University of Rochester. In 1953 he was appointed instructor in medicine at the Georgetown University Medical School; he has headed the radioisotope laboratory at the United States Naval Hospital at Bethesda, Md., since 1953, and he has been director of the radioisotope laboratory at Georgetown University Medical School since 1954.

Dr. Duffy, we are delighted to have you present and to obtain your contribution to this discussion.

Dr. DUFFY. Thank you, sir.

I might introduce my particular brief contribution here this afternoon with a statement concerning the use of isotopes in a diagnosis and treatment of heart disease and cancer.

The specific study that is under way at Georgetown at the present time is the role of radioiodine in the diagnosis and treatment of abnormal thyroid conditions with specific emphasis on the amelioration of incapacitating heart disease. I refer to those cases of severe angina pectoris, or severe chest pain due to coronary insufficiency, and those cases of congestive heart failure where other benefit is unavailing from routine medical means.

We, following out the studies of Drs. Blumgart and Freedberg in Boston, have been interested at the cardiac clinic at Georgetown University, in further evaluating and selecting those cases who will most benefit from this treatment.

In the 127 patients that we have treated results indicate that more than one-half, some 57 percent, of these patients are objectively and subjectively improved.

Representative MILLER. That is with the treatment of calcium 45?

Dr. DUFFY. No, sir, this is with treatment of radioiodine.

Representative MILLER. The isotope.

Dr. DUFFY. Yes. I might say that I was advised that Dr. Geschickter would be speaking on the subject of calcium metabolism, and since my experience has been in the clinical field of cancer and heart disease primarily—starting with the heart first, because I know less about it—I would speak about the use of radioiodine and briefly mention some other medical things we are doing.

Representative MILLER. Are you still carrying on some work at the Naval Research Laboratory?

Dr. DUFFY. Yes, sir.

Representative MILLER. I think it was 3 or 4 years ago I was out there to some symposium on radioactive isotopes. I believe they were using iodine at the time.

Dr. DUFFY. Yes, sir. The big single therapeutic isotope has been iodine, more than probably all the other collected together. This is judged by the shipments from Oak Ridge. Of course, the primary use of iodine is in the diagnosis and treatment of thyroid disease. This has been now extended, as you know, to probably well over 5,000 cases treated.

Representative MILLER. How is it administered?

Dr. DUFFY. It is administered by solution by mouth. It is an odorless, tasteless solution.

Representative MILLER. What type of thyroid do you think it helps?

Dr. DUFFY. The type of thyroid that it helps the most is the overactive thyrotoxic individual, the hyperthyroid patient whose thyroid is working overtime and putting an undue strain on his whole body, including the heart. The group of patients that I originally referred to in this statement, namely, those with advanced heart disease, may not have a demonstrably overactive thyroid gland. But for them their thyroid is perhaps too much of a burden on their heart.

I will just say a brief word about another phase of this work. The studies that we are doing now in cancer that might be of interest are those studies that involve isotopes in the diagnosis of hidden cancers of the brain and liver. This is a great value in the first instance in the brain for helping the surgeon to localize and successfully remove such tumors. We are using radioiodine in the form of iodinated albumin and also phosphorous.

In some institutions these techniques are now routine. We still use them in an experimental way at the naval hospital and Georgetown. But in other hospitals they are done on every patient that is going to go to surgery for a brain tumor.

Although cancer in the liver is not a treatable form it obviously is of great importance to know if it is there. Sometimes it is not otherwise possible to locate it. Secondly, and more importantly, and I think I can summarize the whole cancer issue with this one statement, radioisotopes, to my knowledge and to that of others more experienced, have never proven to be curative in any definite single instance. We have helped some people and you have had testimony that some patients are alive who would not be alive because of the use of radioactive iodine for thyroid cancer and radioactive gold for various forms of disseminated cancers from the ovary, breast, and lung.

These people have repeatedly been helped. They have not been cured because the long road to metabolic localization of enough of the isotope into the area of the cancer to successfully kill all the cancer cells, this road we are only a short distance along.

It is of great importance, it seems to me, that we can diagnostically locate an isotope inside a tumor, and secondly, in the liver tumors we can study the nature of their spread.

Representative MILLER. Doctor, in this diagnostic procedure with the radioactive isotopes to locate a tumor in the brain or liver, what do you use to locate it?

Dr. DUFFY. We use a counter, such as this one.

Representative MILLER. You use a counter?

Dr. DUFFY. Yes. The patient is given an injection of the radioactive isotope, which goes into the brain, the brain tumor tissue selectively picking up this isotope, and the counter can be put on the outside of the intact skull to detect the tumor.

Representative MILLER. You can locate it pretty closely?

Dr. DUFFY. It can be located with a degree of accuracy not otherwise obtainable. It is still a time-consuming procedure. But it is becoming easier. It takes us now only an hour, where it used to take several hours. There are now 3 or 4 large series of patients that have been studied this way.

There is another variant of this. There is another isotope which has been shown to collect very nicely in tumor tissue, but it has a very short range beta ray; namely, radioactive phosphorous. At the time of the operation a sterile probe is inserted right into the brain substance, and by so doing the surgeon can decide whether it is necessary to cut a little bit more or a little bit less. There are neurosurgeons now that don't operate unless they have this technique right at hand.

Representative MILLER. Then I suppose the reaction you get from the counter, you probably get some reaction on the isotope side.

Dr. DUFFY. Yes.

Representative MILLER. It depends on the degree of reaction. You narrow it down because of it, and say it is located here because here is the greatest reaction.

Dr. DUFFY. The area of concentration is the area of tumor. The factor of concentration is usually of the order of 3 or 4 times. We take multiple areas and count over them. If we count over a certain area, and the area counts 1,000 counts, and the rest counts 250, that is the probable area of tumor.

Representative MILLER. I wonder if that could be used with the boron they are using up at Brookhaven the same way?

Dr. DUFFY. The question of combined isotope procedure is a very important one currently being explored. On the *Bennington* cases, for example, who are being treated at the Newport Naval Hospital, they are counting 2 or 3 isotopes in the same burned individual at the same time.

I would emphasize that these procedures have been worked out before.

I refer to the study of the blood plasma and so-called extracellular fluid in these burned patients. Various parts of the body can be studied at the same time with different isotopes.

Representative HINSHAW. We thank you very much, Mr. Duffy. That is a very interesting discussion on a very complex subject, and we hope that some day the answer will be found to all of these things, and yours in particular.

Dr. DUFFY. Thank you, sir, very much.

STATEMENT OF DR. NICHOLAS T. WERTHESSEN, SOUTHWEST FOUNDATION FOR RESEARCH AND EDUCATION, SAN ANTONIO, TEX.

Representative HINSHAW. Now, for a discussion of the use of carbon 14 in the study of leukemia and hardening of the arteries, we have Dr. Nicholas T. Werthessen, of the Southwest Foundation for Research

and Education, San Antonio, Tex. Dr. Werthessen received his bachelor of science degree and Ph. D. degree from Harvard. He served as a research associate to Dr. Gregory Pincus, at Cambridge University, and Clark University from 1937 through 1939. He was director of the endocrine laboratory of the New England Medical Centre from 1939 to 1946. He served as head of the cancer research laboratory of the Worcester Foundation in 1951. Dr. Werthessen has done research in the general fields of endocrinology, cancer, and basic physiology and biochemistry of circulatory disease. He has 35 publications in these fields.

Dr. Werthessen, we are delighted to have you here from San Antonio, Tex., and to contribute to this symposium.

Dr. WERTHESSEN. As the members of the committee may have heard in the past, carbon 14 is an isotope which was probably especially designed for biochemists who have problems outside of radiation. For those workers who are striving to find out what goes on in the human, animal, and plant body it is almost perfect. The virtue of this isotope lies in the fact that its radiation is exceedingly weak. As a consequence it can be expected to do very little, if any, damage to the system being studied. Furthermore, since all biochemical systems involve carbon at some point it follows that we have in this isotope an ideal label that we can tie onto almost every substance in which we are interested. In those cases, such as you have heard discussed earlier, where I–131 and calcium 45 are employed they, too, at some place involve a carbon-containing system. Thus, even when using other isotopes, at some time as the work progresses it will probably be necessary to use carbon 14 to gain a full and complete picture.

The work of our laboratory is in the basic fields. We can say that we are studying the large general problems of arteriosclerosis (more commonly called hardening of the arteries), cancer, and the growth process in general. The manner in which we study these problems calls first for defining the normal situation. The disease state can then be defined in terms of its deviation from the norm. Naturally, to do this we first have to know what constitutes normalcy. We are liable to spend more of our time finding out what is normal than we are in ascertaining what is abnormal.

We can work in two apparently unrelated fields, like cancer and hardening of the arteries, because one substance, cholesterol, and a family of other substances, the steroid hormones, are important in both of these fields. Cholesterol is a compound which seems to accumulate in our arteries as we grow older. As the accumulation of this compound increases, the efficiency of the circulatory system decreases. The compound seems to accumulate in small lumps, which on occasion may become very large, just on the inside of the wall of the arteries. As such, if they did no further harm, these lumps would slow down the passage of the blood, just the way corrosion on the inside of a pipe will keep the water from running through.

I think it is fair to say that it is the general opinion that these accumulations induce the formation of blood clots. Such clots have a nasty tendency to migrate into the coronary and cerebral vessels, and this migration and consequent plugging can cause death. This is probably an oversimplified description of the situation, but I doubt if anyone would want to take the position that hardening of the arteries is not a major factor in circulatory disease.

If it is such a major factor then all the chemical evidence we have today indicates that cholesterol is of prime importance in the situation and we ought to know more about it.

In the field of cancer, a number of workers have found that substances like cholesterol or associated with cholesterol can induce cancer. The structure of cholesterol is such that it becomes a close relative to a number of compounds known to be carcinogenic. When we take a few of the carbons off cholesterol, we obtain steroid hormones. I am leaving to Dr. Schwenk the description of that phase of the situation.

One of the major values of an isotope like carbon 14 is that with it we can demonstrate whether or not a particular reaction or system actually functions in the body. The chemists can work up a number of theoretical reactions and sometimes show that they work in test tubes but only by the use of an isotope can you completely prove that one of these reactions goes on in the body. This is very important, if for nothing else but that it cuts out a lot of speculation and settles issues.

A number of years ago, Dr. Schoenheimer, a worker at Columbia University, was able to show that cholesterol was manufactured by the body. He was also able to show that there were regulating systems and that we excrete about as much of the substance as we take in, in the diet. His students and other workers showed that cholesterol, which contains 27 carbons, is routinely made in the body from acetate which is a 2-carbon substance. Dr. Schwenk will show you what a complicated process this is. Just precisely how this reaction goes forward we do not know. There is a lot of discussion, and the chemists have a great deal of argument about it. The important point from the point of view of this committee, as I understand it, is that very little if any of this work can be done without the use of carbon 14.

Our laboratory being more biologically than chemically minded—that is, we call ourselves physiologists—has been studying which organs can manufacture cholesterol. We have been interested in the processes and situations which affect and regulate the formation of cholesterol. A big help in doing this is that during the past 15 years we developed a technique whereby we can take an organ such as a testicle, liver, ovary, or mammary gland away from the body and keep it alive as long as we wish with a system that substitutes for the heart and lung very well. Through the use of this technique, we have been able to keep human and pig ovaries alive for 3-week periods, and we have been able to see testicles manufacture spermatozoa. But most important of all for this study we have been able to demonstrate that the major blood vessels of the body can manufacture considerable quantities of cholesterol.

Figure 1 (exhibit 69, p. 154) and its legend describe the glass portion of the apparatus.

The real problem in the work is not the apparatus, but getting the system set up without any infection. One single bacterium or fungus that is not susceptible to penicillin or streptomycin would ruin the whole preparation. But my people have become very skillful at this and nowadays we can get out about 7 out of 8 preparations completely free of infection.

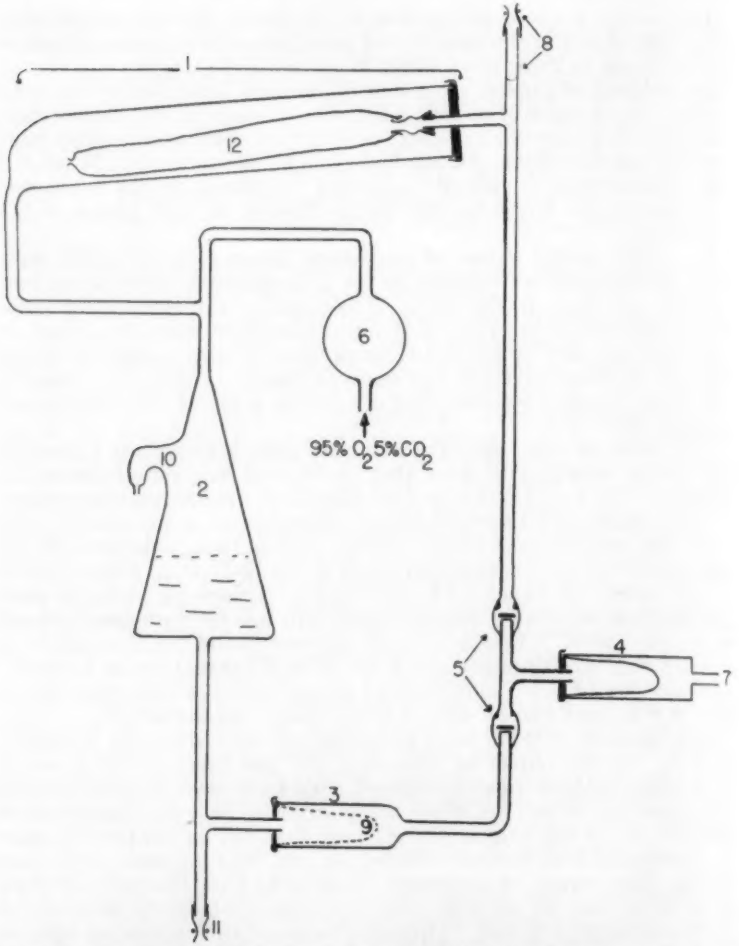

EXHIBIT 69.—Schematic diagram of glass portion of a system capable of use for perfusion of most organs. Chamber (1) designed for perfusions of aortae. Rubber connections between various glass portions found useful instead of making whole apparatus out of glass not illustrated.

Key parts of the system are: (1) organ chamber, (2) fluid reservoir, (3) filtration point, (4) pulsation chamber, and (5) valve system.

Fluid reservoir (2) in diagram consists of a liter Erlenmeyer flask altered. It has been found that the oxygen Co_2 mixture (saturated with H_2O) entering chamber via gas sterilizing ball (6) passing by perfusate at T-tube above reservoir will equilibrate with perfusate with no more area of exposure than indicated in drawing for most organs 50 grams or less.

"Pulsation chamber" (4) and valve system (5) are working portions of the design. Pulsation chamber is a small brass tube. Inside chamber positive and negative air pressure is alternately imposed.

Filtration point (3) contains nylon mesh filter which removes small particles of tissue from perfusate.

By using this technique, we found 2 major points during the past 2 years involving the behavior of cholesterol in blood vessels. This work which I am going to describe was performed in collaboration with Lieutenant Colonel Milch, of Randolph Field, and was supported by Air Force funds.

The first bit of data refers to what are called lipoproteins (exhibit 70, p. 156). They are substances which have occasioned considerable interest in medicine lately because it has been shown that they are liable to be present in high concentration in the blood when there are atheromata in the blood vessels. We have found, as shown by this graph, that this measure of the change in concentration of cholesterol in the blood vessel $\left(\frac{\Delta C}{C}\right)$ is directly related to the amount of change of lipoproteins in the blood that we pump through the blood vessel.

The lower cross in the figure represents one of our experiments that became infected. This point and those represented by the large circles are 24-hour experiments. The upper of the 2 crosses represents a 6-hour run. So perhaps this whole process goes on much more rapidly than we first thought. The important thing is that these data indicate that the lipoproteins are formed by the aorta and may serve as a mechanism for release or deposition of cholesterol from the aorta into the blood stream.

I will have to simply state that there are complications in the biology which may refute this conclusion. And I must emphasize that these are preliminary findings that I am discussing. Future work, as is so often the case in biology, may turn our interpretations completely around.

On the other hand, I feel some security in presenting the data because through the use of C_{14} we have been able to check this point another way.

We perfused an organ for 6 days. Each day we withdrew all the blood running through the organ and replaced it with an equal quantity. To this blood each day we added the same dose of sodium acetate labeled with carbon 14. Earlier, in another experiment we ran an organ for 300 hours, or 12 days. On the 294th hour of that run, we added acetate to the blood system of the perfusion for the first time. We killed the preparation at 300 hours. Thus it had acetate available to it for only the last 6 hours of the run. From that preparation we isolated radioactive cholesterol. Thus from that long experiment we knew that even if the organ was on the pump for 294 hours, it could convert acetate into cholesterol. In the experiment under discussion we are interested in a 6-day performance and not 12.

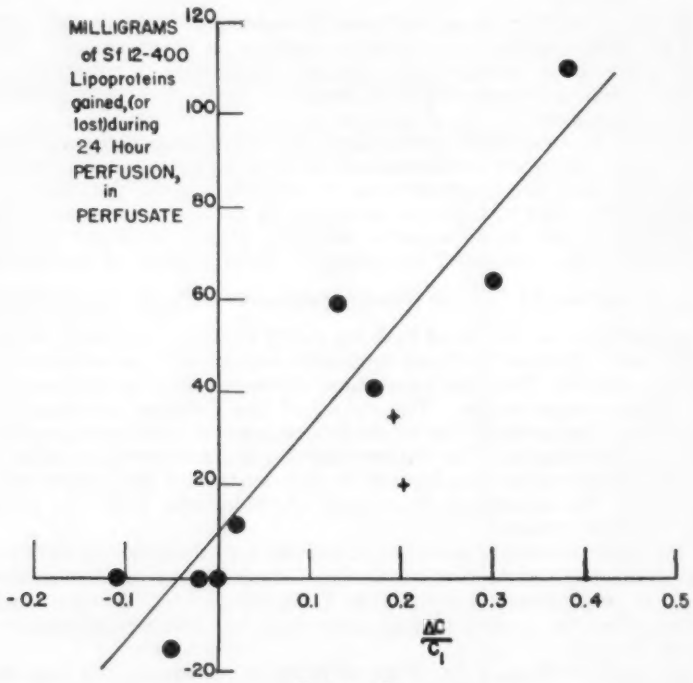

EXHIBIT 70

If an aorta could manufacture cholesterol on the 12th day, then we had plenty of reason to assume that each day of the 12 it could do the same. It follows that if the system is given labeled acetate every day we can expect the cholesterol which is in the aorta to become more and more radioactive every day as new cholesterol made from labeled acetate is added to the cholesterol already present.

Now, remember that we were taking the blood running through the system away from it every 24 hours and that our question was actually "Can the cholesterol come out of the aorta into the perfusate?" If it could, then every day that we measured the radioactivity of the perfusate or blood cholesterol, that activity should rise.

That is what we found. Here as shown in figure 3 (exhibit 71, p. 157) by an entirely different method from that of using lipoprotein assay we are able to show that the aorta can release cholesterol into the blood stream.

Now, let us see how this work applies to the problem of hardening of the arteries. For years people have been drawing relationships between dietary cholesterol and the incidence of hardening of the arteries and fatal heart attacks which could be blamed on this condition.

These studies have been very well founded. They have been supported nicely by observations in the field, in clinics and studies of population diets, and most recently and most importantly by feeding

cholesterol to animals and inducing the formation of hardening of the arteries. It was not until Chaikoff in California was able to show, by the use of C_{14}, that the aorta could manufacture its own cholesterol, that any serious doubt came into the picture that cholesterol in the diet was the primary source of this difficulty. The material we presented here today increases the probability that a revision of the ideas held about atheromata formation may require revision.

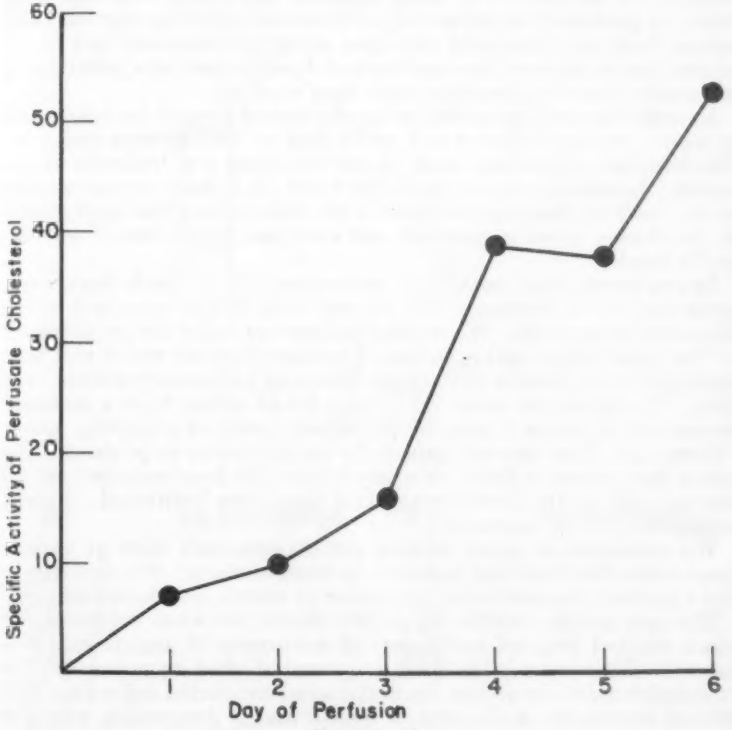

EXHIBIT 71

Let me emphasize however that the data we are presenting here today do not contravene the earlier data. Those data are good. It is the theory that came from the data which may require reexamination. This is what our work seems to indicate.

The changes in the amounts of cholesterol that we are talking about here are too often too miniscule to measure by standard methods. We could not have picked up the increase in cholesterol in the perfusate in the 6-day experiment. We had to have a label on the cholesterol to indicate that it came from the aorta. We cannot work on the same living organ for years in the laboratory, but the process that we are studying takes years and years to become important in the body.

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Through C_{14} we are able to shorten the period of observation and get data that may have meaning.

For the purpose of this hearing, I think I ought to reemphasize at this point that the work that we have done and that Chaikoff and others have done would have been impossible unless C_{14} was available.

The other problem on which our laboratory has worked and used Carbon 14 is leukemia. The development of this problem is a very nice example as to how in a basic research laboratory one can slide from one problem to another and never lose a connecting thread. Our earlier work on cholesterol was done using the liver and had led us to feel that cholesterol was synthesized from acetate at a greater rate when cells were dividing than when they were not.

In order to check up on this point, we looked around for a situation in which we knew there was a great deal of cell division going on. The handiest object that came to our attention was leukemia in the mouse. Leukemia, as you probably know, is a form of cancer that shows itself by flooding the blood with white cells. The background of the disease is not understood, but everyone agrees that it is eventually fatal.

In any event, what we wanted was a situation in which there was a great deal of cell division. We did not think it was important which cells were being made. We wanted further to predict the development of this high rate of cell division. For that the mice which had been developed at the Roscoe B. Jackson Memorial Laboratory seemed to be ideal. To utilize the mice, one takes a bit of spleen from a leukemic mouse and implants it into the peritoneal cavity of a healthy mouse. Fifteen days later one can expect the second mouse to be dead. The tumor has grown so large, so many white cells have crowded out all the red cells in the bloodstream, and they have infiltrated so many organs that life is impossible.

We proceeded to inject labeled acetate into such mice at various times after they had had leukemia induced in them. We expected to find a marked increase in the conversion of acetate into cholesterol.

The next graph (exhibit 72, p. 159) shows you what we found. It was a marked drop off in the rate of conversion of acetate into cholesterol. This curve is the exact reciprocal of what we expected. We expected to start low and go up, and instead we started out with a high rate of conversion in the control mouse, and it dropped to very low levels by the time the animal had leukemia for 200 hours.

As I said earlier, in order to induce leukemia, we had to take a piece of infected spleen and implant that into the healthy animal. In checking into the problem, we thought it would be worthwhile to treat animals with spleen from a healthy animal and spleen from an animal with leukemia. The next graph (exhibit 73, p. 159) shows you what happened there.

The black dots refer to animals that received healthy spleen. The crosses and dash lines refer to animals who received spleen plus leukemia. It is very clear from these data that spleen or spleen plus leukemia reduce or at least affect the conversion of acetate into cholesterol.

Through the use of these data we may have a mechanism by which other workers may be able to study leukemia a little more efficiently than they are doing today. In order to study leukemia today from

the chemotherapy point of view it takes 15 to 20 days to run an experiment. Through the use of these data on cholesterol formation here, we may be able to provide a shorter type of test.

Incidentally, you may all have heard a good deal about the effect that spleen has in protecting an animal from radiation damage. As I saw from the program this has been gone into fairly considerably.

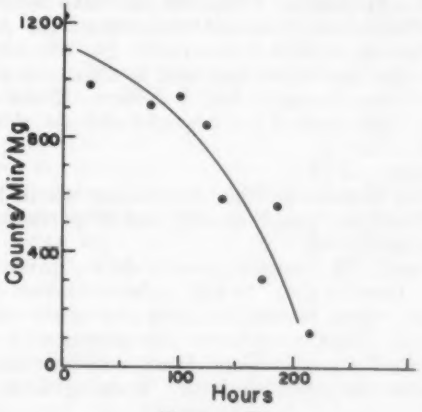


EXHIBIT 72

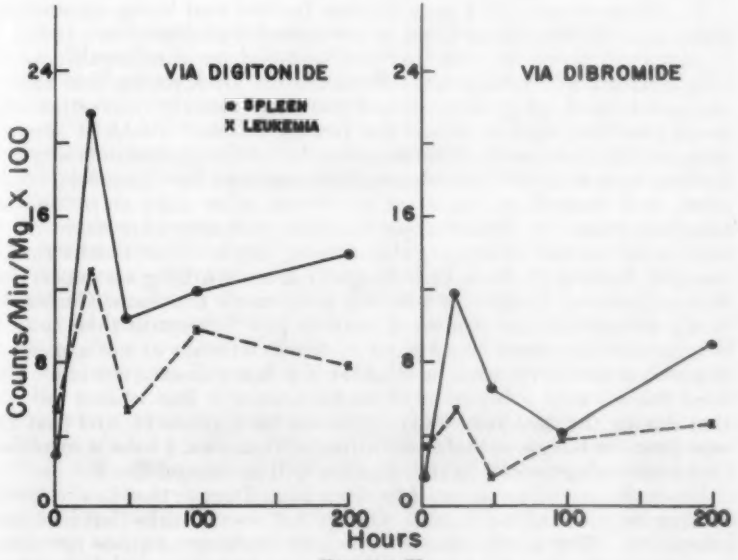


EXHIBIT 73

Representative HINSHAW. Yes, we heard it discussed yesterday to our great interest.

Dr. WERTHESSEN. I will not go too far with this except to say that some data that we have indicates that radiation may have an effect on the conversion of acetate into cholesterol. This is the opposite direction of the spleen effect. So naturally we are going to chase this down.

Representative HINSHAW. I suppose you have been apprised of the work of Dr. Hasterlick, associate director of the Argonne Cancer Hospital in Chicago in that connection. He was here on yesterday and explained that radiation damage, in this case also to a mouse, was fairly well compensated for, I believe, if the spleen was removed—that is, not excised, but brought outside of the body of the mouse—and shielded.

Dr. WERTHESSEN. Yes.

Representative HINSHAW. Then the mouse would be irradiated as much as 1,000 roentgens and they only had 20 percent casualties when the spleen was protected.

Dr. WERTHESSEN. If I may digress from my prepared talk at this point, what we hope to do is to take spleens and set them up in our perfusion pump where we do not have any other organs around to confuse the issue. Then we can treat the spleens with what you might call radiated blood (that is blood from a radiated animal) and we can try to isolate the principle which is doing what Hasterlick has described.

Representative HINSHAW. That will be very interesting indeed.

Dr. WERTHESSEN. If I may digress further and bring up another point I would like to say I am in a wonderful position here, today, I hope, to get across a point that has bothered me considerably as an administrator of a laboratory. We scientists are learning that money makes a laboratory go around, and you people on the committee may be an excellent place to attack for further funds. The AEC, beginning in 1948, as a part of its program for utilizing atomic energy to further cancer research, made available isotopes for diagnosis, treatment, and research in cancer at no charge other than shipping and handling costs. In 1953 isotopes for these purposes were made available at 20 percent of the regular catalog price. This means that I can buy Carbon 14 from Oak Ridge if I am working on cancer for $8 a millicurie. Unfortunately, if I want to use that same Carbon 14 in my arteriosclerosis studies, I have to pay $32 a millicurie, and it becomes awfully hard on occasion to decide whether or not a piece of research is cancer research or whether it is heart disease research. So far I think I have nobly resisted the temptation. But when I tell you that during the past year we spent $1,800 for Carbon 14, and that for next year the budget calls for a tripling of that sum, I have a suspicion that restraining myself in this manner will be more difficult.

Representative HINSHAW. I have an idea, Doctor, that in the forthcoming revisions of the Atomic Energy Act we will take that into consideration. The whole committee is now working on those revisions, and I know that it is the idea of all of us to add to the work being done with radioactive isotopes and, of course, if we can add to the work by reducing the cost, that will be a good idea. At the same time we have decided, I believe, that we don't want to provide them for no cost,

although we could, because undoubtedly they would be wasted by some or perhaps hoarded.

Dr. WERTHESSEN. My own feeling on that thing is that charging the $8 for a millicurie is a very good procedure, because if you pass out to lab technicians and others substances which cost nothing, they will be liable to spill them a bit more easily than otherwise.

Representative HINSHAW. That is what we have thought.

Dr. WERTHESSEN. There is one other point here. I do not know whether or not it has come to your consideration. We have to have a chemist in our laboratory to convert Carbon 14 into acetate. The reason we have to have him is that acetate as it is commercially available is $200 a millicurie. There are two suggestions that I would like to make on this score. I think you can see the reason for them when I tell you about a particular study we have in progress. This study is in essence taking our in vitro data, the test tube data, and trying to apply it to the whole animal. We are studying the aorta. It is a small portion of the whole animal. It is a tissue that does not respire too actively. In order to work on that animal we have to give it a half millicurie per kilo. A rabbit may weigh as many as four kilos. So that even at $32 a millicurie it sometimes comes out that we have to pay $50 for the acetate that we put into that animal at the very beginning.

Statistics being what they are, no matter how you twist and squirm, you have to use 5 to 10 animals per point. This gets to be a very sizable item. So it works out that for that 1 small project I have to have a budget of $3,000 for Carbon 14 in the form of barium carbonate at $32 a millicurie.

There is another factor here which I think is important (and you probably realize it) and that is that the funds for the kind of work I have described are largely derived either from taxes or from donations on the part of the people. I was wondering if it would be within the area of the AEC to think about the problem of making available to laboratories such as mine things like acetate on a different basis than they are today and to somehow bring the price down from $200 a millicurie.

The reason I bring it up is that the conversion of carbon from the form of barium carbonate into acetate is a process which, if my chemist has a good day and everything goes well, is 90 percent efficient. He is one man doing this. He is fortunate. We use it in large quantities, and because of that the efficiency is better. It is usually closer to 80 percent if small quantities are used. The net effect is that if the AEC supplies 100 millicuries to people using acetate, between 80 and 90 millicuries get into actual experiments. That is 10 to 20 millicuries wasted, and no one can get hold of them again.

There is also another point which I think is important, and that is that we cannot, because of the technical problems involved, say flatly that we are injecting a half millicurie per kilo. We have to extrapolate our data back to what the Oak Ridge people say they have sent us, and as we compute the yield. To be precise, we should measure it, but we cannot because we cannot afford all the complicated instrumentation and physicists that are required.

I would like to bring to you the thought that for this kind of basic, nonprofit research the making available of some kind of agency which

would permit us to use internationally or nationally standardized acetate would be very helpful. Then I can say that Dr. Schwenk, working in Worcester, Mass., is using a millicurie which is the same millicurie that I am using in San Antonio, Tex. It would help tremendously. I think it would increase the overall efficiency of the program.

Representative HINSHAW. Doctor, that is a very fine contribution to both our knowledge and thinking. We feel indebted to you for the presentation. Do you have any questions, Dr. Miller?

Representative MILLER. I hope you get through with your studies on cholesterol and find out how important it might be to blood pressure. As we get older, we increase our cholesterol. You showed the aorta; of course, cholesterol can be manufactured in any vessels or even the muscles of the body.

Dr. WERTHESSEN. That is right.

Representative MILLER. Even though they are functioning normally? The doctor before you spoke about spinach and rhubarb controlling calcium and probably having some effect on cholesterol. Have you examined that facet of the problem?

Dr. WERTHESSEN. We have one bit of data that I did not bring forward because of the time factor, and that is that by inducing high blood pressure in these systems we produce more accumulation of cholesterol than when we run at low pressure. I think you will agree with me that the standard clinical concept is that first come the atheromata or the atherosclerosis, and then the heightened blood pressure. These data indicate it is the reverse. If that is the case, one of the best methods of attack would be to take the average overworked individual and keep his blood pressure down whether he likes it or not.

Representative HINSHAW. That is a very interesting thought, Doctor, and I hope it is pursued to find out whether it is actually the case or not. It sounds reasonable.

STATEMENT OF DR. ERWIN SCHWENK, WORCESTER FOUNDATION FOR EXPERIMENTAL BIOLOGY

Representative HINSHAW. Now we have Dr. Erwin Schwenk, who has been introduced in part by Dr. Werthessen. Dr. Erwin Schwenk of the Worcester Foundation for Experimental Biology will discuss the use of radioactive carbon in research on steroids.

Dr. Schwenk is a native of Prague, Czechoslovakia. He received his engineering degree at Technische Hochschule, Vienna, in 1909, and his Doctorate in Technology, the following year. He was assistant chemist at the State School of Wine Growing in Geisenheim, Germany, from 1910 to 1912. He was on the staff of the institute of bacteriology at the University of Erlangen, Bavaria, from 1912 to 1913 and assistant teacher at the School of Leather Chemistry in Vienna in 1913–14. He was assistant at the Kaiser Wilhelm Institute in Berlin from 1914 to 1916; director of research at the Verein for Chemical and Metallurgical Production in Aussig, Czechoslovakia, from 1916 to 1928. He was assistant director of research at Schering A. G., in Berlin from 1928 to 1933; director of research and vice president of the Schering Corp. from 1938 to 1948; and has been a consultant to the Schering Corp. from 1948 to 1953. He joined the staff of the Worcester Foun-

dation for Experimental Biology in 1949. He served with the Office of Scientific Research and Development. He is a member of the American Chemical Society and the Institute of Chemical Engineers; a fellow of the New York Academy; a member of the American Academy of Arts and Sciences at Boston and the London Chemical Society. He is research professor of organic chemistry at the Boston University. Dr. Schwenk's fields of research include anthraquinone and indigo vat dyes; azo dyestuff intermediates; sex hormones and steroids; protein-like hormones; camphor; antihistamines; spasmolytics, and analgesics.

Dr. Schwenk, we are delighted to have you here and in spite of all those peculiar words, I hope I have not mispronounced too many of them.

Dr. SCHWENK. Mr. Chairman, you have pronounced them very well. With your permission, before I go into the middle of my discussion, I would like to mention two points which I think are more or less fundamental.

I show you here two substances. If I would have given these two substances 20 years ago to the best chemist in the country, he would have come up after a certain time with the statement that these two substances are identical, that they cannot be distinguished. Their properties as far as chemistry goes, are completely the same. There is no way of telling them apart; if we mix them we would not be able to separate them again.

Today when we hold the one substance to the Geiger counter, we will hear nothing. The other substance, however, as you see and hear shows radioactivity. This experiment may explain how we use radioisotopes in our scientific work. Any substance which contains radiocarbon will not be distinguishable from the same substance which does not contain radiocarbon. It is important that the living cell in the body of animals or plants also cannot distinguish the radioactive molecule from the nonradioactive and consequently reacts completely normally to it as if there were no radioactivity present. So if we in the course of our experiments are able to introduce radiocarbon in the place of ordinary carbon into a compound, we will be able to follow this compound by its radioactivity through any of its reactions, without interfering with the normal life processes of the animal or plant.

Now about the introduction of radiocarbon into a molecule—how is that done? I have here a model which represents the substance which I intend to discuss later. This is cholesterol about which you have heard before from Dr. Werthessen, a very important substance in biology. In this model of cholesterol the black balls represent carbon atoms, the white ones hydrogen and the one red ball oxygen. How can we introduce radiocarbon in such molecule? We can break the molecule in any part—demonstration—such as this, eliminate this carbon, put in the place of this ordinary carbon atom a radiocarbon atom and then close the ring again. Thus we will have the molecule labeled in one special point in the first ring.

We can do the same thing elsewhere in the molecule as for example in this appendix which we call the side chain. It can be cut off piecemeal and any of the carbon atoms can be replaced by a radio carbon atom. This synthetic way of labeling a substance is paralleled by the

labeling by biosynthesis. When we feed a plant CO_2 containing radioactive carbon the plant will synthesize as usual sugar—hexose—from it, and this sugar will contain radioactive carbon. We shall later hear more about this biological way of labeling as far as cholesterol is concerned. If such a labeled compound is used in experiments and the body destroys this molecule in some unknown way, we may be able to locate the radio carbon atom by its radioactivity.

The second point which I want to make is that most of the reactions with which we are concerned in biological experimentation are so-called steady state reactions, or reactions which do not result in a net change of the concentration of reaction products. If the body contains cholesterol, and each of us contains about 200–210 grams of this substance, this value is at least during adult lifetime quite constant. Synthesis and degradation are taking place concurrently and balance quite well, so that this figure of 200–210 grams remains unchanged.

That is the reason why we cannot see anything that happens in the body while a reaction is going on. What we do with our compounds with radioactive carbon is similar to experimentation which has been done with rivers in a desert. A river will disappear in a desert, and to find out the way which the water takes in the soil, we throw a certain dyestuff in, and the dyestuff is dissolved and carried along. Then when several miles away we find 2 or 3 different rivulets coming out of the soil we can distinguish which comes from the first source because it will carry the dyestuff. We can determine in this way the time the water spends under the earth.

The biological experiment is quite similar. If we introduce not a dyestuff but radioactively labeled substances into the body, they are carried along through the path of biosynthesis and come out as a finished labeled product. We can measure and establish by this method what is happening between the starting material and the end product.

The group of substances about which I have to talk today is known under the name of steroids. This name is derived from the most important member of this group. It is cholesterol which I showed you before in this model, and which is presented on this slide No. 1 (exhibit 74, p. 165), on the right side here.

Representative MILLER. Did you say there were 200 grams of cholesterol in the normal individual?

Dr. SCHWENK. In a man.

Representative MILLER. What is the normal amount in the bloodstream?

Dr. SCHWENK. In the bloodstream?

Representative MILLER. Yes.

Dr. SCHWENK. In human beings it is about 200 milligrams per 100 cubic centimeters of blood. This figures fluctuates some in nature. There are people who have a little more and people who have a little less. That is about the average.

Representative MILLER. What does it mean if you have a low cholesterol or a high cholesterol?

Dr. SCHWENK. The cholesterol contents of the blood is one of the figures which I would say is among the most stable in life. In his blood an adult man may have, say, 180 milligrams. He will have that practically all the time, as I mentioned before. Even if he eats a

large amount of cholesterol-giving food, like eggs, it will not change his blood cholesterol very much in a short time. Naturally, when it goes for many years, the amount may increase. We know that a certain number, I think it is about 70 percent of the people, have in old age an increased amount of cholesterol in the blood. This fact has been connected with the appearance of arteriosclerosis.

I would say on the substances which I talk about, they have this so-called four-ring system. In cholesterol there is what we call a side chain attached to it which consists of a straight string of carbon atoms. The different steroid compounds are all derived from the same four-ring system by changes in it and by changes involving the side chain.

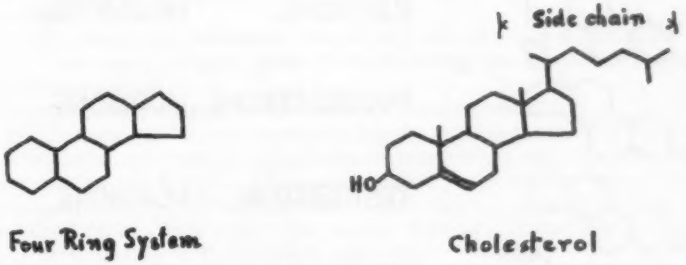


EXHIBIT 74

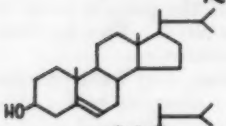
To show the importance of the steroids in nature, I have chart No. 1 (exhibit 75, p. 166) which contains the most important substances of this group. You see the first substance is cholesterol. Here it is only a representative of a large group of natural substances which differ from cholesterol very little. They occur not only in animals, but also in plants, down to the smallest living organism. I will have the occasion to say more about this, but the very interesting thing is that cholesterol is characteristic for animals, that there is no animal which does not have cholesterol as the most important steroid. In plants, however, we have usually a number of steroids present. So we have in the soybean the sitosterols and in yeast ergosterol which you have heard about because it is a precursor of vitamin D, which is shown as the next substance in the chart.

We find a great number of such sterols as cholesterol down to the fungi and the small organisms consisting of single cells.

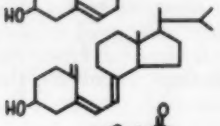
The next group of substances in the chart consists of four which are here as representatives of the hormones. The female sex hormone which determines the female body is estrone, the pregnancy protecting progesterone and testosterone, characteristic for the man and finally cortisone as an example of the hormones of the adrenals.

The next group are the bile acids represented here by cholic acid. We know cholesterol in the body is converted into such bile acids by cutting off the side chain here at this point. The bile acids are extremely important in metabolism, in digestion. Up to now it is unfortunately the only well known fact about cholesterol, that it is converted into bile acids in the body continuously and excreted with the bile into the intestine to help in the digestion of food.

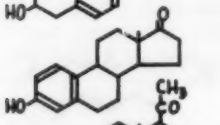
NATURAL SUBSTANCES CONTAINING THE CYCLOPENTANOPHENANTHRENE RING SYSTEM



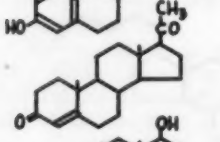
CHOLESTEROL



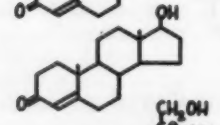
VITAMIN - D_3 VITAMIN



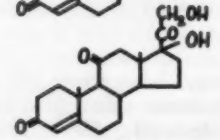
ESTRONE HORMONE



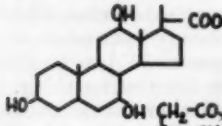
PROGESTERONE HORMONE



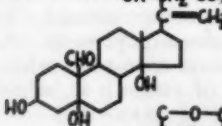
TESTOSTERONE HORMONE



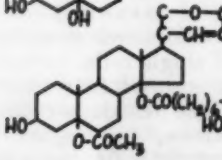
CORTISONE HORMONE



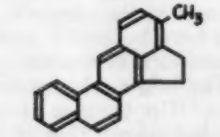
CHOLIC ACID BILE ACID



STROPHANTINE PLANT CARDIAC



BUFOTALINE ANIMAL CARDIAC



METHYLCHOLANTHRENE CARCINOGENE

EXHIBIT 75

The next two substances in the chart are so-called cardiac substances which act on the heart; they are used in medicine. I have put in a plant cardiac, strophantine, and an animal cardiac, bufotaline. This latter has been used as a medicine for many hundreds of years by physicians in Asia in the form of a concoction made from the skin of certain toads.

The last substance here is derived from cholesterol by bending the side chain over and forming a new six ring. This substance is called methyl-cholanthrene. When we inject this material into an animal, or paint an animal's skin with a solution of this substance, there will be cancer developed in the place, or elsewhere in the body of the animal.

Representative MILLER. How many carbons are there compared to cholesterol?

Dr. SCHWENK. Cholesterol has 27 and this one has 6 carbon atoms less. You see this part goes off (indicating on model). It closes something like this.

Representative MILLER. And that is carcinogenic.

Dr. SCHWENK. This substance is highly carcinogenic, and with 1 or 2 other substances which have been isolated from coal tar, this is the most active substance. This same substance has been prepared in this country by Professor Fieser synthetically, and it can be also prepared from a bile acid. So we see there is a connection and intimate relationship with the other steroids.

I would like to emphasize that the importance of these substances is not restricted to their scientific use because commercially I would say the substances in this chart may represent about $200 million business for the pharmaceutical industry of this country. So they are quite important.

I would like now to show how important was the introduction of radioactive precursors for the study of the biosynthesis of these substances. About 20 years ago, the late Professor Schoenheimer had the idea to test labelled acetic acid as a starting material in the body. He and his co-workers Rittenberg and Bloch proved that acetic acid is the starting material in the body, very probably for cholesterol and a number of other important substances. I have to say that in the body we have a pool of acetic acid. There is always a certain amount of acetic acid present which is derived from either the food or from reactions in the body. There is one very important question. (Demonstration.) This is a model of acetic acid, a substance which contains two carbons (black balls), four hydrogens (white balls) and two oxygens (red balls). How can from this simple substance be derived this molecule of cholesterol which contains 27 carbon atoms?

We do not know anything yet how this is coming about. We know a little more about how the same acetic acid can be used in the body as a starting material for fatty acids. Fatty acids have a molecule containing for example 18 carbons, which are strung up like pearls on a cord, and they have at the end this same grouping as you see here in acetic acid. So if I would take these 2 carbons apart and insert between them 16 carbons we would have a formula of a fatty acid (stearic acid), the main constituent of the solid fat of the body of animals.

How is this brought about? This is brought about by the combination of nine molecules of acetic acid head to tail as shown in the next chart No. 2 (exhibit 76, p. 168). Always the first carbon atom

of one molecule binds itself to the second carbon of the other molecule. The oxygen containing group at the end is preserved in this process, while the other oxygen atoms are replaced by hydrogen, thus forming the straight chain as you see on the chart.

If we now take this molecule of acetic acid and make it radioactive if we use one which has a radio carbon here, we find the following peculiar situation. This last carbon of the fatty acid at the end of the molecule here has the highest count. If we cut up the whole molecule piecemeal we will find that if this carbon atom on the right end has a count of 100, another uneven numbered carbon further up the chain will have only 50 counts.

In cholesterol, however, all the radio carbons in the molecule have the same count. When we use acetic acid labeled in one carbon only in an experiment with an animal or in plants, and isolate the sterol then we find that every second carbon atom in its molecule is radioactive just like in the acetic acid with which we started. So it must be that the acetic acid goes into the molecule, as such, and possibly in one reaction, not like into the fatty acids in a sequence of steps, which gives the body time to dilute the intermediate substances with the substances which are present in the body anyhow.

EXHIBIT 76

Dr. Werthessen has told you a little about the impurities in the cholesterol. One of the discoveries which helped us much was that when cholesterol is formed in the body of an animal like a rat or in perfusions of isolated organs like the liver, then there is always a certain amount of companion impurities which count much higher than the cholesterol which is formed. We have a method of separating the companions and the cholesterol. If we take for instance the biosynthesis of cholesterol in the blood cells as shown in slide No. 2 (exhibit 77, below), we see that both the companion impurities represented by the upper curve and the cholesterol represented by the lower curve start out simultaneously. After a certain time the cholesterol continues to increase steadily at the expense of the companion impurities.

We have taken this peculiar situation as supporting the idea that the companion substances represented by the space between the two curves may be precursors of cholesterol in its biosynthesis.

What could that mean? I would like to remind you of the experiment which I mentioned before with the river in the desert. We pour our labeled acetic acid into the course of the biosynthesis at one point, and this radioactivity goes through until it appears in the final end product the cholesterol. The substances between the two as shown in the next chart No. 3 (exhibit 78, p. 170), which are here put in as crosses because we do not know what they are, these substances correspond to the fore mentioned companion substances. We call them precursors, because when we isolate them—and we have methods to separate them chemically in groups, then we can take the substances which are represented at this point by a cross and feed them to an animal, and this will again make radioactive cholesterol. That is proof that we have true intermediates in the biosynthesis of cholesterol because they are still convertible into cholesterol.

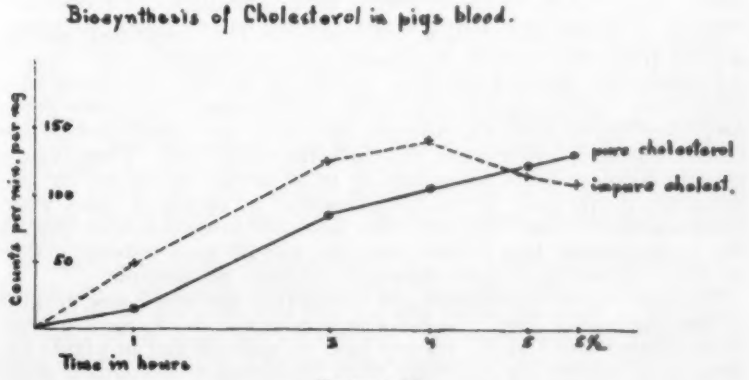


EXHIBIT 77

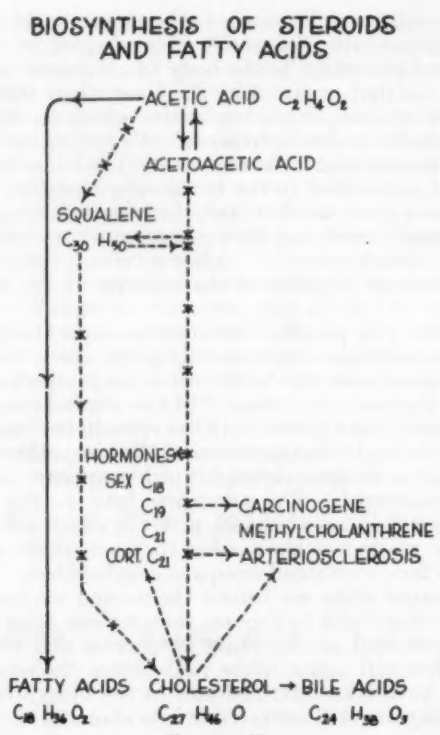


EXHIBIT 78

Only one substance of these precursors has been identified, and by several different groups in this country; it is called squalene. This is a hydrocarbon, again a substance consisting like the fatty acids of a long chain containing 30 carbon atoms. Squalene was known for a long time before these experiments because it is a constituent of the oil of the livers of certain fish, especially the shark liver. These organs contain large amounts, sometimes up to 40 percent of their liver material being squalene. It has been observed by people at times when there was no radioactivity and other means of modern science that in the young animal there is more squalene, and little cholesterol, and in the older animal there is less squalene and more cholesterol.

We have found with radioactive carbon that squalene is also formed in the mammalian liver. Radioactive squalene is also formed in yeast from labeled acetic acid. So you have in animals and in plants the same very interesting substance with 30 carbon atoms which when given to the animal is converted into cholesterol in much better yield than is acetic acid. While of acetic acid only a fraction of 1 percent is converted to cholesterol and the rest is partly excreted as carbon dioxide and partly converted into other substances in the body, of squalene at least 10 to 15 percent are converted into cholesterol directly.

This is extremely important; and still more important it becomes because we know that squalene, and that is pure chemistry, can be derived from another hydrocarbon which contains only 5 carbon atoms. Six such units form squalene. This hydrocarbon is called isoprene and isoprene is one of the starting materials for natural rubber. In fact, the Germans during the first World War started to make rubber from isoprene. There is a very peculiar connection now with our biosynthesis problem. Rubber is made in plants. Indeed, when you take the leaves of the Guayule plant which is a rubber producer and put them in a medium containing radioactive acetate then the rubber made in these leaves is radioactive. Like rubber all the terpenes including camphor and menthol are isoprene derivatives. So we have a wonderful correlation between the animals and the plants, both make the same substance squalene from radioactive acetate, possibly through isoprene as first product.

I have mentioned before that in yeast acetic acid is converted into another sterol called ergosterol, which has the same general structure as cholesterol but contains one more carbon atom. If the biosynthetic processes from acetic acid to ergosterol in the yeast are the same as the processes from acetic acid to cholesterol in the animal, then it should be possible to show their identity with radioactive acetic acid. Indeed we find that when the radioactive companion impurities obtained from yeast are fed to a rat they will produce in this animal radioactive cholesterol but not ergosterol. So the plant makes the same intermediate material as the animal. Only in the last sequence of reactions it is converted in the plant into ergosterol instead of into cholesterol.

May I have the next slide No. 3, please (exhibit 79, p. 172), which is due to Dr. Werthessen.

This drawing on the left side represents the situation of the liver in the body of an animal. This is the liver and here the heart which pumps the blood around through the different blood vessels, the veins and arteries. Now we take the liver out by cutting these blood vessels as shown in the right upper corner. Finally we put the liver as shown in the right lower corner in a glass apparatus. This is the organ chamber which you have seen in Dr. Werthessen's slides to contain the aorta, and we connect to a pump which pumps the blood used to carry oxygen and food around. Such an arrangement is a perfusion of liver which allows to reproduce the situation of the surviving liver without interference with any of the other parts of the body of the animal.

When this experiment was done, it was found to our great surprise that a pig liver which we took out of the animal and which without much delay—was put into the apparatus would show a very low synthesis of cholesterol from acetate. However, when the liver was damaged by cutting it or by putting a culture of staphylococci into the circulating blood or by just leaving it for a time before the experiment the cholesterol synthesis would increase considerably.

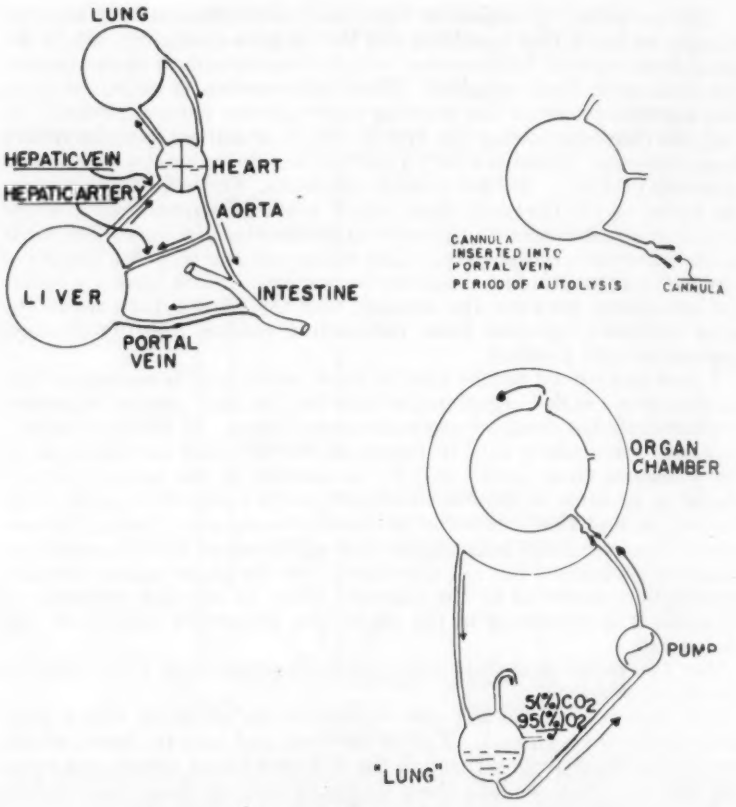


EXHIBIT 79

You will see the influence of such damage depicted in the next slide No. 4 (exhibit 80, p. 173). In this experiment where the liver was just left for different time intervals the cells suffer because of lack of oxygen and autolysis. You will see that the efficiency with which cholesterol is made from acetate goes up rapidly when this damage increases with time. This may have some pathological or medical importance, because in sickness or in old age we can possibly assume that the liver also suffers damage and that its synthetic and other abilities may be altered. In all liver perfusions the cholesterol contained higher counting companion impurities. A number of other organs like the ovaries, the testis, the adrenals or the aortas, which Dr. Werthessen has shown us before, also produce cholesterol and companion impurities when perfused with radioactive acetate. One can probably say that all cells of the body are inherently able to synthesize cholesterol from acetate. Now when we inject radioactive acetate into a living rat then we find that all organs in the animal contain radioactive cholesterol. We find, however, also that each organ evidently has a very specific pattern to transform the acetate into cholesterol. Liver and

intestine contain the largest amounts and so seem to have the highest velocity with which this reaction is carried out, while the skin, the blood, or the remaining carcass evidently have a much slower rate of synthesis. These latter organs, therefore, contain much smaller amounts of cholesterol than liver or intestines. In the liver of the rat we have practically no companion impurities but they are present in the intestine. We assume that this is so because the liver produces cholesterol so fast that the companion impurities cannot accumulate. Only 10 to 15 minutes after injection of the acetate large amounts of cholesterol are found in the rat liver. The intestine with a lower and slower rate of synthesis preserves the companions much longer, before converting them further.

The liver also destroys or uses cholesterol for other reactions very fast; an hour after the injection of the acetate a large part of the newly synthesized cholesterol has disappeared.

In another animal species for instance in the guinea pig we find a different situation. The liver produces much less cholesterol than in the rat and slowly enough to preserve the companion impurities for a certain time before converting them into cholesterol.

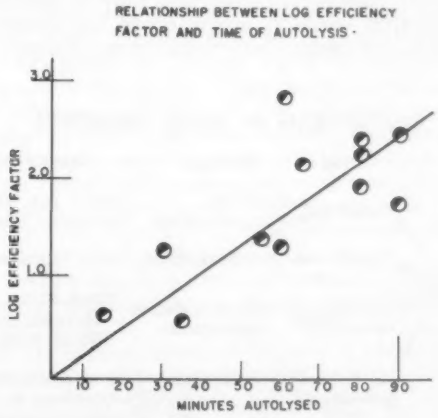


EXHIBIT 80

This difference of cholesterol metabolism between the rat and the guinea pig may have some special significance. The rat when fed for sometime large amounts of cholesterol does not show arteriosclerotic changes, while the guinea pig does under similar conditions. It is very probable that the rat liver, which, as I said before, can destroy cholesterol very fast, is able to cope with large amounts of cholesterol better than the guinea-pig liver with a much slower cholesterol destruction rate. Man may also in older age become unable to cope with cholesterol because liver may be less ready to destroy the accumulating excess of cholesterol, which may then make arteriosclerosis possible.

Let us now turn to this chart No. 4 (exhibit 81, p. 174), which has 4 columns. In the second are the different tissues or organs which convert acetate into the products of the third column and in the last

column are some of the characteristic functions of these products. Most of the conversions in this chart have been established by the use of radioactively labeled acetate in perfusions or similar experiments with the organs outside of the body of the animal from which this organ was taken. When for example an ovary of a sow was perfused with blood containing labeled acetate, radioactive estrone was formed, proving that the ovary can make estrone from acetate. The ovary, however, also produces at the same time cholesterol and so it could be that first cholesterol is made from acetate and this then further transformed into the hormone. That this is not so was shown in a pregnant mare. The urine of this animal contains large amounts of the female sex hormone which is commercially prepared from such urine by several pharmaceutical houses. If a pregnant mare is injected with labeled acetate then the hormone isolated from this urine is radioactive, while when radioactive cholesterol is injected, the estrone is devoid of radioactivity. There is, therefore, no doubt that cholesterol is not the precursor for estrone. We believe it possible that the companion impurities, the precursors of cholesterol in the biosynthesis may be the material from which the estrone arises. On the basis of other experiments, however, cholesterol may be converted into the pregnancy-protecting hormone progesterone, the second in this chart. The testis transforms acetate into testosterone, which is the male sex hormone.

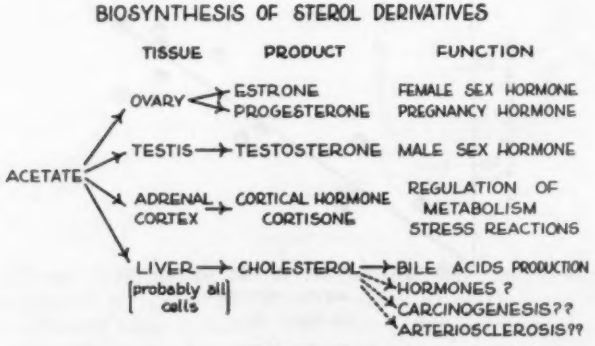


EXHIBIT 81

The reactions which occur in the adrenal glands during perfusion with labeled acetate have been for several years a special field of investigation for the Worcester Foundation. A large number of substances have been identified in these experiments besides some of the most important adrenal cortical hormones, thus giving insight into the complicated reactions occurring in these glands. These hormones, for example cortisone, have found a large use in rheumatoid arthritis and other conditions. The equally important relationship of these hormones to the protection of the body in stress situations including irradiation damages is also studied extensively in the Worcester Foundation. The question whether these hormones can be made from cholesterol in the gland cannot be answered definitely at this time.

Finally we have on this chart No. 4 the conversion of acetate by the liver or other cells in the body to cholesterol. What is now the function of this substance of which we have heard so much today? Only one function is established beyond doubt: labeled cholesterol is converted to a large degree into bile acids in the body of animals and man. These acids as constituents of the bile are essential in the digestion of fats as food. Other reactions mentioned before as possible but not established are the conversion of cholesterol into hormones and its possible role in the development of arteriosclerosis. It has also been accused as a carcinogenic substance on the basis of animal experiments. But this is by no means clear. It may very well be that it is the companion impurities and not cholesterol itself which must be suspected in this connection.

We can say that in view of the questions which still await solution only very little has been done up to now in our field. If, however, what has been done has any value, it is due to the preparation of the radioactive substances by the AEC. Not much could have been accomplished without these precious compounds. We are sincerely grateful for the opportunity which we had to use radioactive material in our work. Thank you.

Representative HINSHAW. That is a very amazing discussion, Doctor. We are certainly grateful to have it and all the work which was done in years gone by. If you scientists can possibly find out the ultimate answers to some of these questions before this career, like all of our careers, is terminated, you will have made a contribution in your lifetime that is beyond anything that has been made so far. It is certainly an amazing chain of things that I as a layman had not realized before, although I am sufficiently acquainted with such things to know it when I see it. It is a very close approximation of molecular form that I don't think most of us realized before. What do you think about that, Dr. Miller?

Representative MILLER. It is most interesting. I think it impresses me that the human machine is not only a mysterious one, but almost frightfully constructed in some ways. There are so many things that we do not understand about it. I said I would come over here for an hour, but I have been so absorbed in this thing that I have stayed and I appreciate the opportunity of being here.

Representative HINSHAW. Thank you very much, indeed, Doctor. Dr. SCHWENK. Thank you.

STATEMENT OF DR PAUL K. SMITH, PROFESSOR OF PHARMACOLOGY, GEORGE WASHINGTON UNIVERSITY SCHOOL OF MEDICINE, WASHINGTON, D. C.

Representative HINSHAW. Now, as a final addition to this splendid symposium, we have the subject of the use of radioisotopes and synthetically labelel compounds in medical research, discussed by an eminent pharmacologist, Dr. Paul K. Smith, a professor of pharmacology, George Washington University School of Medicine. Dr. Smith was born in Missouri, and received his B. A. degree from Westminster College, and his Ph. D. from Yale University in 1934. He was assistant in biochemistry at the Yale University School of Medicine from 1932 to 1934, fellow in pharmacology from 1934 to 1936

and instructor and assistant professor from 1936 to 1941. Dr. Smith served for 5 years in the Air Corps where he worked at the aeromedical laboratory, Wright Field, in the early part of the war; and later he became chief of pharmacology and biochemistry at the AAF School of Aviation Medicine at Randolph Field. He was appointed professor of pharmacology at George Washington School of Medicine in 1946. He is a consultant in therapeutics at University and Gallinger Hospitals and consultant in radioisotopes at the Martinsburg Veterans Hospital. His scientific societies include the American Chemical Society, Sigma Xi, Society for Experimental Biology and Medicine, American Society for Pharmacology and Experimental Therapeutics, Aeromedical Association, Academy of Medicine, Washington, D. C., American Association for Cancer Research, American Association for the Advancement of Science, and the Radiation Research Society. Dr. Smith's research interests include electrolyte and water metabolism, analgesic drugs, physical chemistry of proteins and amino acids, biological application of radioisotopes, motion-sickness drugs, drug metabolism, chemotherapy of cancer, biological effects of radiation, and chemotherapy of virus diseases.

Dr. Smith, we are very glad to have you as a contributor to this very worthwhile symposium. We are sorry only that more of us can't be present to hear this presentation. But, as you know, they are engaged elsewhere.

Dr. SMITH. First I want to express my admiration for the fortitude of our chairman. I have been around here at intervals for 3 days, and I know quite well what he is going through.

Representative HINSHAW. I do not consider it fortitude, my dear sir. I consider it something of extreme interest, and something in which I personally am interested, although I am a layman, and I trust that by my being a layman, instead of a professional man, that I can force you gentlemen into speaking a language which is understandable to the lay public.

Dr. SMITH. It is very kind of you to hear us through. The only assurance I can give you is that your ordeal, or your pleasure, as you will, is almost over.

First I should say that I suspect that history will show that the furnishing of radiocarbon by the Atomic Energy Commission has in itself been one of the greatest contributions to medical research in our time and for a long time to come. These remarks complement to a great extent those of Dr. Geiling's of yesterday. One principal difference is that Dr. Geiling spoke of biologically labeled drugs whereas I shall speak of drugs prepared synthetically in the laboratory. Most of these are prepared with radiocarbon. Of course, as you know, we are particularly fortunate that radiocarbon has a so-called half life of 6,000 years. That is, if we had 100 atoms today, 6,000 years from now we would still have 50 atoms.

This long half life of carbon is not quite as fortunate a circumstance as we thought in one respect. That is, we may synthesize a drug, and then it proceeds to knock itself out due to the explosion of the radiocarbon atoms in it. This is illustrated with this chart (exhibit 82, p. 177) on which are drawn 5 molecules of methanol. 1 labeled with radiocarbon. When the radiocarbon atom explodes it not only destroys itself, but many of the surrounding molecules,

so that you end up with a series of substances, such as ordinary methane, water, and glycol, which are different from the original starting material. This presents one difficulty we must constantly strive to overcome and that is to maintain the purity of these compounds. Even the compond we made last year may not be the same as this year, so we have to purify it again.

What I am going to do now is to give you several examples of the use of synthetic drugs with radioactive isotopes and I want to stress that these are only examples, because the work we have done and the work of others that I shall tell you about, represent only a very small portion of the excellent work that is going on in this field.

The problem of the synthesis of these compounds may be illustrated by the synthesis of aspirin because it is one of the few times we can start with the material as it comes directly from Oak Ridge in the form of barium carbonate, react it with acid to get radioactive carbon dioxide, which we can combine with phenol, and by a unique reaction, the carbon dioxide goes into the molecule to form salicylic acid (exhibit 83, p. 178). This radioactive salicylic acid is labeled at one specific point. We can then react that with a substance known as acetyl chloride, and get radioactive aspirin. By exactly the same process, we can start with radioactively labeled acetyl chloride, and end up with the label in the acetyl group. In this way we have a powerful way of determining precisely what happens to the molecule after it is taken into the body.

By the way, I chose aspirin for 3 reasons; 1, because we have worked on it for a long time; another, because it is the most widely used drug in the world; and the third, and not least, because it is an excellent relief for headaches and we understand congressional committees have many of these.

Representative HINSHAW. We thank you for recognizing that.

Dr. SMITH. We are able to give this substance to normal subjects because by this specific labeling we can give such a small amount of the radiocarbon compound that there seems to be no danger whatever to the subject, provided he does not take too many doses of it.

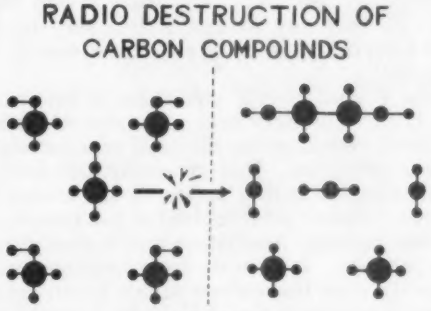


EXHIBIT 82

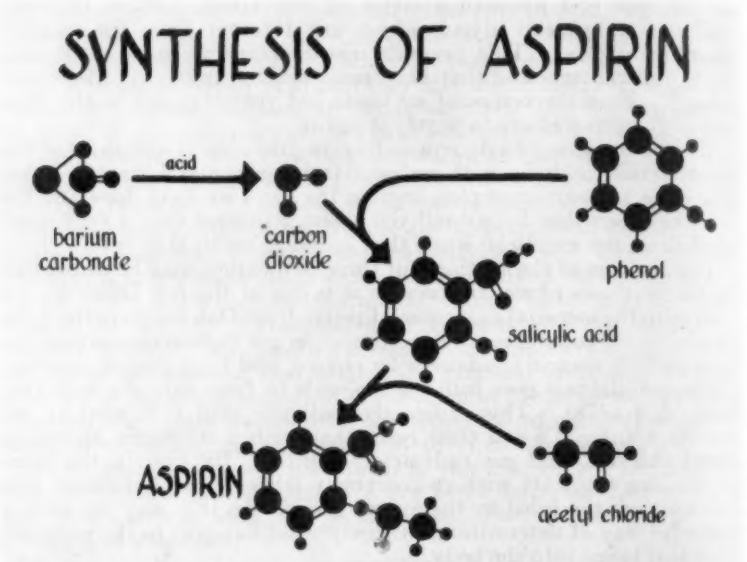
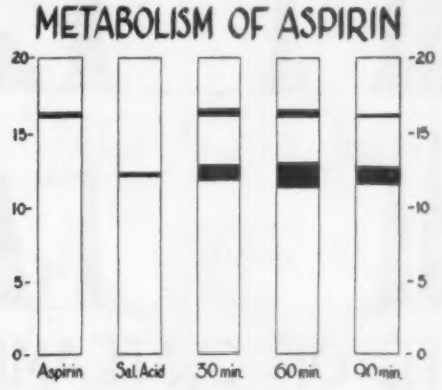


EXHIBIT 83

First of all, we give this compound to normal subjects, and then take blood samples at intervals and separate the plasma, and then we can show by a process known as paper chromatography exactly how rapidly the aspirin is broken down in the body (exhibit 84, p. 179). It will move along through the filter paper to a certain position in a certain time. Salicylic acid only moves this far. But if we take a sample of blood from subjects 30 minutes after giving the drug, we find that it has some aspirin and some salicylate and 60 minutes some aspirin and more salicylate, and finally there is very little aspirin left in the plasma. In this way we can follow very nicely the rate of decrease of the aspirin in the body and know exactly what happens to it.

The next drug I want to tell you about is known as cysteamine (exhibit 85, p. 179). This substance is the one which so far has been the most effective in reducing the effects of irradiation, whether from X-rays or nuclear radiation. Unfortunately, one must give it to the animal before irradiation so that makes its use in civil defense of not much consequence. But it is being used at the present time in cancer patients who must undergo irradiation and it does diminish the toxic effects in these patients. It is made from hydrogen sulfide which we can produce readily from the barium sulfide furnished by Oak Ridge. It is such a simple synthesis that I thought I would show it to you. It gives us a very nice compound in a short time. When we give this to animals or people we find that it is oxidized very extensively. We separate it out by a process comparable to filter paper chromotography known as ion exchange chromotography (exhibit 86, p. 180). If we are able to make a guess as to what compounds are formed, we can

synthesize them in the laboratory to see if they match up. If we put in a known compound and it comes out at the same point as a peak of radioactivity we can be fairly certain they are identical. If it comes out here it is cysteamine sulfoxide. If it is here, it is cysteamine, and over here it is cystamine. Here we have more radioactive humps than we can account for so we have more work to do.



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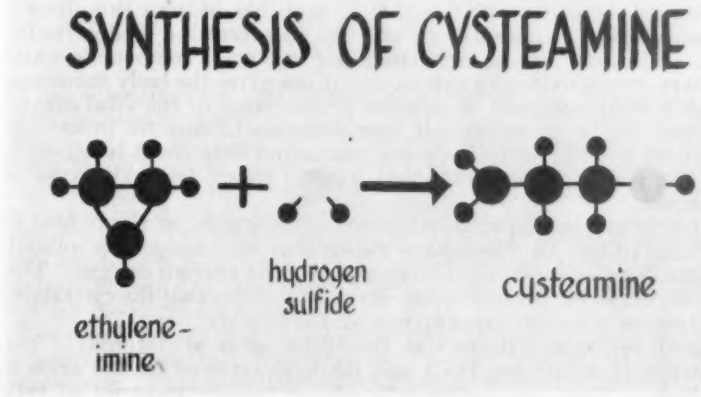


EXHIBIT 85

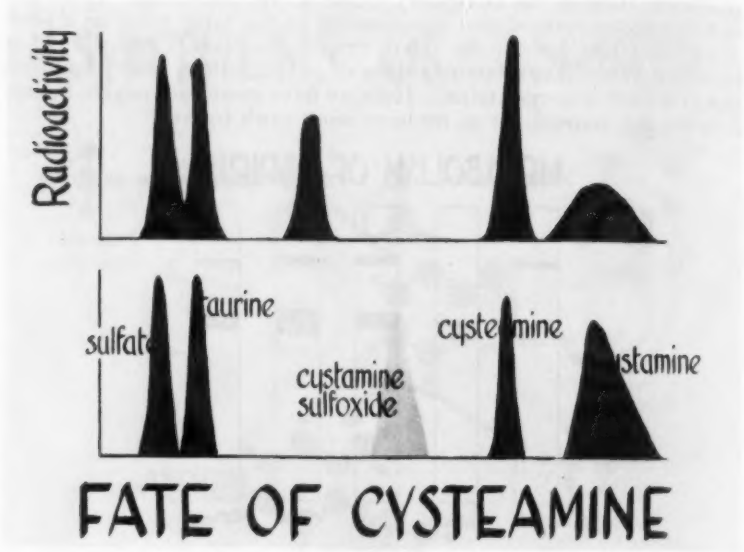


EXHIBIT 86

All these compounds represent several stages of oxidation. Sulfate represents complete oxidation. It is probably because this drug is so easily oxidized that it is so effective in protecting against radiation. When the body is irradiated, it forms some compounds which are very strong oxidizing agents, and if one gives the body something which is easily oxidized, it seems to protect some of the vital enzyme systems. So far as we can tell, that is the mechanism for protection. What we would like to have is a compound that could be given at just the proper time, and which would protect from all types of radiation.

I might say in that connection that some studies at the School of Medicine of the Air Force have shown that you can protect animals against irradiation simply by not giving them enough oxygen. This partial protection fits in every nicely with the idea that the cysteamine acts because it readily takes up oxygen in the body.

I shall return to a theme that Dr. Mider spoke of yesterday. You remember he mentioned DNA and RNA, as types of nucleic acids in the body. These are components of the nuclear material of cells intimately associated with the chromosomes, and therefore with the hereditary characteristics of the cell. By introducing small subunits of the nucleic acids, such as guanine, we are able to trace its incorporation into the nucleoproteins of normal animals and of animals with tumors, and we are able to show also how quickly it is broken down once it is incorporated. We have been able to show that the breakdown is speeded up by exposing the animal to X-rays.

Another important aspect of this has been to demonstrate that we can prepare what are called antimetabolites and block the utilization of normal substances in the cell. That is very important from

the standpoint of retarding growth of a tumor. I call your attention to the structure of this compound known as guanine and this compound known as azaguanine (exhibit 87, below). Each of them has a radiocarbon atom at the same point, but the normal one, guanine, has a carbon atom at a certain position, and the other one, azaguanine, has a nitrogen at the same position. This compound is so much like guanine that it fools the cell partially and the cell takes up the unnatural form and blocks the enzyme system in the cell so it is not able to take up the normal component. This interrupts growth with the subsequent death of the cell.

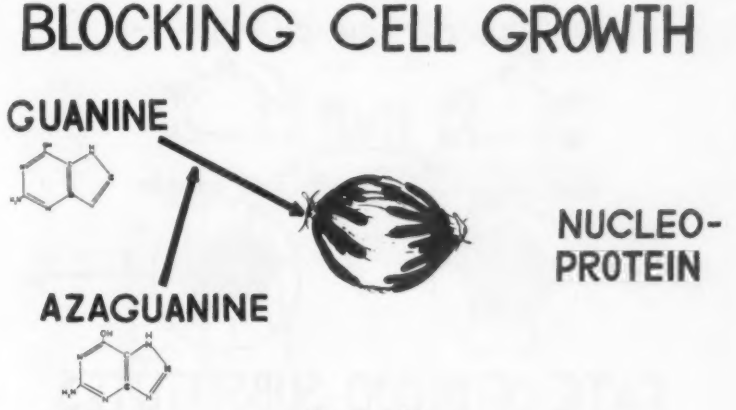


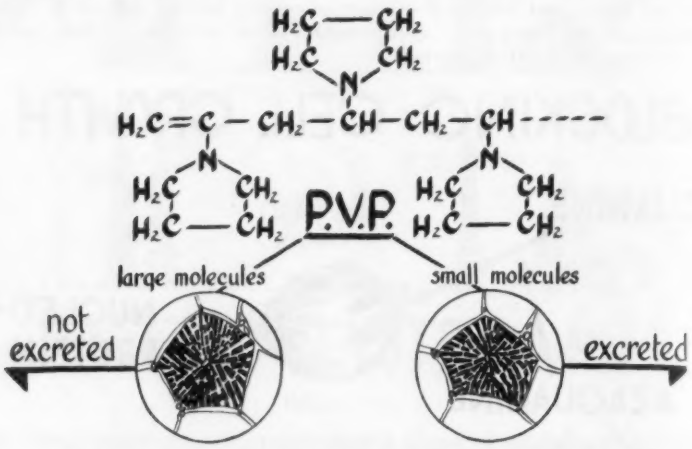
EXHIBIT 87

Time is getting late, and I just want to tell you about some studies that have been done relating to the treatment of shock. As you know, shock is one of the most serious consequences of any type of grave injury to the body, and if it is not treated immediately, death ensues in a relatively short time. For the treatment of shock with the attendant loss of blood, whole blood is still the best therapy. But it is very difficult to have whole blood of the proper type at the proper time, so there has been a great deal of interest recently in the preparation of compounds that will serve as temporary substitutes for blood, or at least for blood plasma.

The one I want to tell you about next, because use of the labeled compound has been very helpful, is one known as PVP, or polyvinyl pyrrolidone. This substance was first used by the Germans for the treatment of shock and it worked very well. Then it was shown that certain batches tended to remain in the body for a long time. It has been with the aid of the radiocarbon labeled material that we found out just why this is so.

I call your attention to the structure of the compound (exhibit 88, p. 182). This is not the end of it; it goes on and on. It is a polymer: that is, it is a compound of many similar units. There are three units shown here. The important point is that if you add too many units and make too large a molecule, it works fine as a plasma expander in the therapy of shock, but it cannot be excreted by the kidneys, and studies of patients have shown that after as much as a year or more, there are deposits of it in the liver.

The diagram represents just a single lobe in a small portion of the liver, and you may see the deposits here, whereas if the molecules are not made so large, it is excreted, and you do not find deposits of it in the liver. I believe that this has been an important contribution because in practice it is practical to cut off the chain at about the right length and give us a blood substitute which has the desired characteristics.



FATE OF BLOOD SUBSTITUTES

EXHIBIT 88

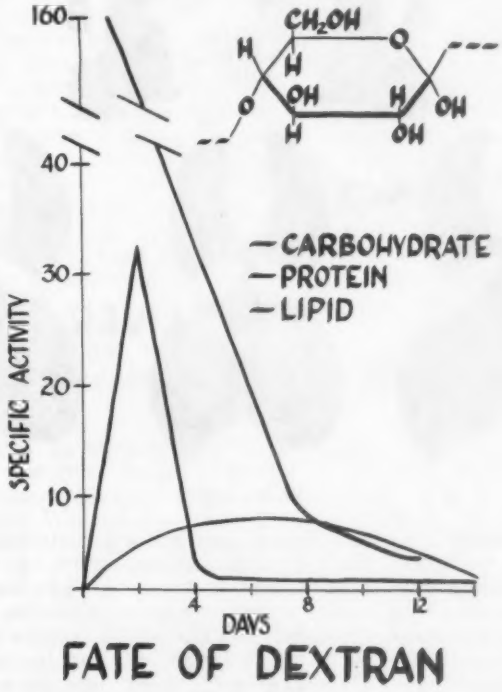
In the same connection there has been another compound produced by a certain bacterium that is useful in preventing shock. This substance, known as dextran, resembles starch in many ways, because it too is a polymer, of ordinary glucose. This compound has been prepared with radiocarbon, and it has been shown that in spite of giving it intravenously, as of course must be done in the therapy of shock, it is slowly broken down in the body, yielding carbohydrate, protein and fat. From the diagram (exhibit 89, p. 183) you may see that part of the dextran goes to carbohydrate, so that at the end of 1 to 2 days you have a large amount of labeled carbohydrate. The fat is formed slowly and metabolized very slowly. The protein is formed and broken down at an intermediate rate. The important point is that after 2 weeks there is no appreciable amount of radioactivity left, so one can be quite sure that neither the liver nor any other vital organ is blocked. This is certainly in favor of the extensive use of and stockpiling of this compound.

Representative HINSHAW. That is a substitute for blood again?

Dr. SMITH. That is again a substitute for blood, or more specifically for blood plasma, because we still do not have the pigments for the transport of oxygen.

Another study associated with the problem of transfusion is of a rather different nature. It has been known for a long time that when a patient is badly injured, if you give him blood, he is much better off

because the red cells of the blood are able to function in the recipient for a long time. On the other hand, it has become known only fairly recently that this is not true of the white cells. If you give white cells from one patient to another, even without taking it out of the body first, but by direct transfusion, the white cells stay in the lungs, and in fact if you give enough white cells, they will begin to interfere with the normal respiratory function of the lungs. (Exhibit 90, p. 184)



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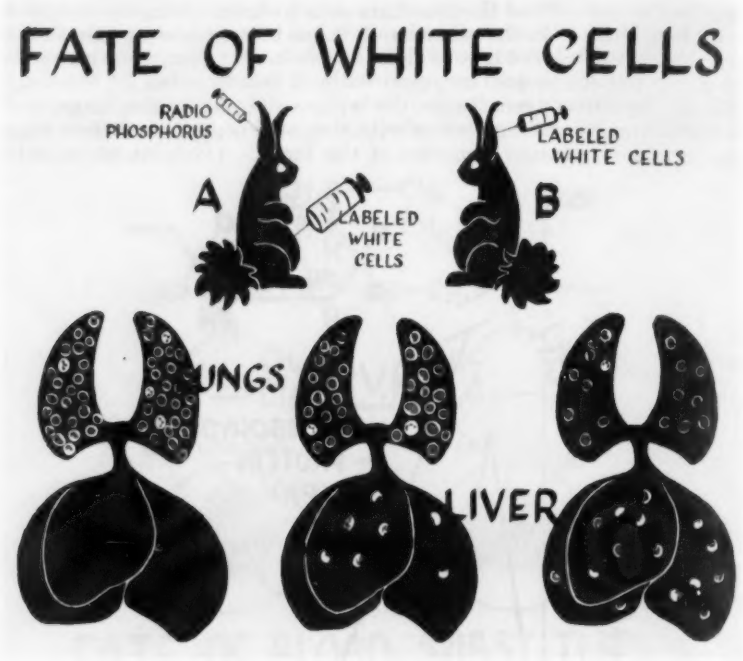

EXHIBIT 90

What is more important is that they are not contributing in any way to the welfare of the recipient. As you know, the white cells are very important from the standpoint of resistance to disease. They would be particularly useful in damage after radiation, because in radiation as you know, the spleen and the bone marrow are damaged, so the white cells are lost to a greater extent than the red cells. I think the experiments illustrated may be of some interest to you. Although they don't solve the problem, they show a promising approach. If one takes a rabbit and gives him a large dose of radiophosphorus, and some time later taps his belly, one can remove a large number of white cells which migrated there. These white cells are well labeled with radiophosphorus. They can be washed free of the contaminating radiophosphorus and injected into rabbit B. When this is done, we find, interestingly enough, that all of them at the end of 5 minutes are in the lungs.

After 3 hours we find that some of the radioactivity is in the liver, and a little less in the lungs, but we find that the substances in the liver do not represent entire white cells. In other words, they are merely fragments, and therefore not functioning white cells at all.

Even after 24 hours, we find more radioactivity in the liver than in the lungs, but again only mere fragments of white cells. So all we know about this problem at the present time is that we cannot transfuse white cells successfully and we do not know why. We wish we knew more. We are trying to irradiate the lungs of animals to

see if that in itself will cause them to release the white cells. That is one possibility that has not been explored. All of this latter work was done at one of the Veterans' Administration hospitals nearby.

The time is getting late and I just want to remind you, gentlemen, that these are just little bits of research, and many, many other laboratories are carrying out similar investigations. All are made possible through the furnishing of these radioisotopes by the Atomic Energy Commission. They are of great help and assistance to all of us. Thank you.

Representative HINSHAW. Dr. Smith, we thank you a great deal for coming today and giving us the benefit of your work and your study. It has been very profitable, indeed. If there is one thing that this hearing or this symposium has brought out, it is the fact that a great deal of work is being done, and some progress is being made. While it does not always show in a forward direction, it can at least rule out paths that are unprofitable for someone else to follow. Certainly the profitable paths can be marked, and others can go ahead in those directions. The numbers of paths to follow in all of these research items are, I am sure, far greater than the number of those who are able to follow them. So there is much work yet to be done for not only this generation, but coming generations.

STATEMENT OF DR. JOHN C. BUGHER, DIRECTOR, DIVISION OF BIOLOGY AND MEDICINE, ATOMIC ENERGY COMMISSION—Resumed

Dr. BUGHER. In the foregoing presentation, the rapid evolution of the atomic energy program in medicine has been portrayed. From small beginnings, substantial gains have already been achieved.

Dr. Shields Warren sketched for you the philosophy behind the inception and early development of the AEC's medical research program, and how our direct interest in cancer research, with the special encouragement by the Congress in 1948, has resulted in a strong and unique research effort in the cancer field.

Dr. John H. Lawrence, who first administered an artificially produced radioisotope to a patient, has recounted the early pioneering with limited supplies of radioisotopes, equipment which was relatively crude by present day standards, and available financial support limited indeed. He has also told how, in the modern Donner and Crocker Laboratories at the University of California, Berkeley, atomic energy byproducts are being used in the study and treatment of leukemia, polycythemia, hardening of the arteries, and a variety of diseases.

Dr. Marshall Brucer has told of the program developed at the Oak Ridge Institute of Nuclear Studies. This program is predicated on the institution's physical proximity to the Oak Ridge National Laboratory where the Commission's program in the production of radioisotopes is centered. He recounted the concerted effort at Oak Ridge to exploit to the greatest extent possible radioisotopes whether pile made or from the fission product wastes from the AEC's production reactors. They have used them in the treatment of cancer by teletherapy, by brachytherapy, and by internal administration. He indicated how the participation of industry will make these advances more rapidly available to the medical profession.

Dr. Farr has shown how, with the atomic tools available at the Brookhaven National Laboratory, he has been able to apply a basic

interest in the way chemical elements distribute themselves throughout the human body to the development of a new technique in the treatment of brain cancer, namely, the neutron capture reaction by boron 10. This work, now in its fourth year, grows more rather than less promising with time and it is our hope that the work can be expedited and the applications broadened by making available to Dr. Farr at an early date a reactor designed especially for medical uses.

Last Wednesday afternoon, Dr. Hasterlik presented the highlights of the research effort at the Argonne Cancer Research Hospital in Chicago. He mentioned the broad implications of work directed originally toward developing a treatment for radiation injury. He described the efforts of this group in improving and developing teletherapy techniques and equipment, using specifically Co^{60} sources, and a new 60 million electron volt linear accelerator.

He also explained the saving in gross weight of shielding material for teletherapy sources which can be gained by using metals of high atomic number such as uranium. With lighter shields, it is possible to design simpler and more easily maneuverable devices for rotational teletherapy.

He has shown you the small radiothulium diagnostic X-ray unit for field use developed by the Argonne National Laboratory.

Professor Geiling has shown before your very eyes how he incorporates radiocarbon into a digitalis-like drug in the living toad. He has indicated how these techniques of biosynthesis have been applied in the study of drug action and of the means by which the body disposes of drugs.

I have discussed one of many ways in which radiological techniques may be applied to the study of the transmission and epidemiology of disease. Many difficult field problems in public health can be readily solved by the general use of the new procedures. They will be especially valuable in resolving the medical problems confronting great masses of people in the so-called undeveloped areas of the world.

Dr. Mider, of the National Cancer Institute, and Dr. Kety, of the National Institute of Mental Health, have broadened the future of medical applications into other areas of medical researches. They have underlined how the availability of the new tools has enabled the scientists at the National Institutes of Health and the United States Public Health Service grantees all over the country to get on with their important researches with greatly increased productivity.

On the third day you heard from Drs. Geschickter and Duffy, of the Georgetown Medical School, that the availability of radiocalcium has simplified the fundamental studies of the role of calcium in health and in disease. Similarly, Dr. Werthesen, from the Southwest Foundation for Research and Education, has shown how essential radiocarbon is to the work he is doing on heart disease and diseases of the blood vessels. He made a special plea that the AEC assistance in isotope procurement now given to cancer investigators be extended to all medical research. His point is well taken and this matter is under consideration by the Commission at the present time.

Dr. Schwenk, of the Worcester Foundation, has related something of the unique work of that institution in determining the modes of action of the steroid sex and adrenal hormones.

Finally, Dr. Smith, of the George Washington University School of Medicine, has shown how drugs can be labeled in the test tube as opposed to the biological methods outlined by Dr. Geiling. He has shown also how drug action can be studied and improved upon by exploiting radio tracer techniques.

This bombardment of scientific data aimed at depicting the impact of radioisotopes and radiation techniques on the medical sciences has been leavened by the deep enthusiasm of the scientists themselves. Government can create opportunity; but accomplishment depends on the zeal and dedication of the individual scientists. Programs have meaning only in human terms. Ultimately our responsibility lies in maintaining the equable climate in which productive scholarship can flourish, where original ideas are welcomed and where the dissenting voice can be heard.

The Division of Biology and Medicine of the AEC looks forward to the steady advancement of knowledge in the medical sciences, through its on-site research programs in the national laboratories, its special cancer research facilities and major projects at university medical schools, through its sponsorship of off-site research projects at universities, hospital, and independent medical research laboratories.. It functions, not in isolation, but in close collaboration with all other agencies of relevant interests. Through its program of fellowships in industrial medicine, industrial hygiene, and radiological physics, it forges the links between knowledge and practice.

In the immediate future certain trends in our research effort will be apparent. Emphasis is shifting from crude or gross radiation effects to the more subtle and intimate intracellular biochemical processes. We will emphasize work directed at understanding causative mechanisms, with special attention to radiation as a coagent, in the production of cancer. We must acquire more knowledge of environmental factors as they affect health. The development of new diagnostic techniques will continue.

In therapy, especial emphasis will be placed on neutron capture techniques and in the utilization of radioisotopes in kilocurie quantities for external radiation. The momentous advances in accelerator design will be adapted to medical purposes as rapidly as possible.

This program, one of the major peacetime applications of atomic energy, has far-reaching international impact. In cooperation with the scientific efforts of other nations, the development of medical science to the general benefit of man should be greatly accelerated.

Representative HINSHAW. Thank you very much, Dr. Bugher. This completes our presentations.

We are very indebted to all of you for your contribution to this hearing. The committee, and the chairman in particular, is indebted to Admiral Calver, our Capitol physician, for suggesting today's list of eminent personalities.

I would like to assure each of you individually, that although the full committee itself is engaged in the hearing on the general bill, and consequently the numbers appearing to hear you are small, that the numbers who will receive this information through publication of the hearings is quite large indeed, and they will be at liberty to sit down and more leisurely go over the discussions which you have offered for elucidation.

Thank you very much, indeed, all of you.

(Thereupon at 4:50 p. m., Friday, June 4, 1954, the hearing was closed.)

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